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ABSTRACT

This report studies the effects of marihuana on the individual's physical and psychological health, as well as the effects of cannibas use on the society. A major purpose of this report is to serve as an up-to-date compendium of scientific information bearing on the issue of marihuana and health. In order to make the report maximally useful to the technically trained as well as to the layman, findings are reported in technical as well as in more everyday language. The report attempts to carefully describe the strengths and limitations of the work that has been done in this area. The authors of the report state that with the increase of our knowledge of marihuana and its effects, we have become increasingly capable of better designing research so as to more adequately answer the many questions that its use poses in American society. This report emphasizes the more recent findings and their significance in the light of our past knowledge. (Author/WS)

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MARIHUANA AND HEALTH

SECOND ANNUAL REPORT TO CONGRESS

from

The Secretary of Health, Education, and Welfare

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TABLE OF CONTENTS

	Acknowledgments	2
I.	Introduction	3
II.	Summary	8
III.	Extent, Patterns and Social Context of Use in the United States	31
IV.	Marihuana Use in Other Countries	54
V.	The Material and Analytic Methodology	133
VI.	Preclinical Research in Animals	157
VII.	Tolerance	189
VIII.	Effects in Man	199
IX.	Therapeutic Uses of Cannabis	259
X.	Future Research Directions	269

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Dr. Monique Braude - Sections on the material, analytic methodology, preclinical studies in animals, pharmacological aspects of tolerance.
Miss Eleanor Carroll - Section on cannabis use abroad and the historical portion of the section on therapeutic uses of cannabis.
Dr. Alan Ramsey - Section on the Effects in Man, viz: acute physical toxicity, chronic physical effects, genetic & birth defects, and psychiatric illness and contemporary aspects of therapeutic use.
Dr. Louise Richards - Section on Extent, Patterns and Social Context of Use in the United States.
Dr. Jean Paul Smith - Discussion of impurities and adulterants in the section on the Material and Analytic Methodology.
Dr. Stephen Szara - Section on the Effects in Man, viz: the active ingredient, route of administration, metabolism, subjective, physiological and biochemical aspects, intellectual & psychomotor effects.

Dr. Robert C. Petersen edited and coordinated the preparation of the report in addition to preparing the introduction, summary and section on future research directions.

I. INTRODUCTION

INTRODUCTION

This marks the second in a series of reports prepared in accordance with the "Marihuana and Health Reporting Act" (Title V of P.L. 91-296). Under this act the Secretary of Health, Education and Welfare has the responsibility to submit annual reports to the Congress on the health consequences of marihuana use. "Health consequences" for the purposes of this report include not only the effects of the drug on the individual's physical and psychological health, but also the effects of cannabis use on the society.

Our knowledge of marihuana has significantly increased during the past year. A serious problem in evaluating research in a socially controversial area such as this is the ever present temptation for many to over generalize far beyond what the research warrants. Each new finding is eagerly sought after and the limitations of any single study are too often overlooked.

There are two important difficulties in the interpretation of much drug research. One is that drugs as investigated in the laboratory are not used under the same conditions as are to be found in illicit social use. Under more typical use conditions marihuana may be used along with other drugs and the social context of use may profoundly alter the individual's response. When cannabis use is studied in cultures that are different in many ways from our own, the implications of use may be quite different from that in American society. For example, the performance demands made by an agrarian society like that of rural Jamaica are quite different from those made by a modern, industrial society.

Each of the various research approaches has both advantages and disadvantages. The limitations of each is to some extent compensated for by the strengths of the others. When the observations derived from clinical observations, systematic laboratory research and cross cultural observation all converge toward a common conclusion, we can have far greater confidence than that possible based on a single study.

The dilemma posed by present and future marihuana use in our society can only partially be resolved by scientific evidence. The issues profoundly involve questions of values, social custom, legal controls and our often inconsistent view of recreational drug use including that of alcohol and tobacco. These larger issues are appropriately the concern of all segments of society and are currently being considered by many other groups including a Presidential Commission. We have attempted throughout the report to limit ourselves to those issues on which a scientific judgment is possible leaving examination of other, equally important, social, political and economic aspects of use to others.

A major purpose of this report is to serve as an up-to-date compendium of scientific information bearing on the issue of marihuana and health. In order to make the report maximally useful to the technically trained as well as to the layman we have reported findings both technically and, wherever possible, in more everyday language.

Because of the tendency for many reports to overgeneralize conclusions based on single studies, we have attempted to describe carefully the strengths and limitations of the work that has been done. With the increase in our knowledge of marihuana and its effects we have become increasingly capable of better designing research so as to more adequately answer the many questions its use poses in American society. This year's report emphasizes the more recent findings and their significance in the light of our past knowledge.

Sources of Information

An unusually wide variety of sources of information have been used in the preparation of this report. These have ranged from published and unpublished reports from scientists to information supplied about local marihuana use by our embassies abroad. In addition to reports from the scientific literature, much of the report is based on formal and informal reports from grantees of the National Institute of Mental Health and researchers who have been supplied with marihuana and related materials by the Institute. They in turn have been generous in sharing their often quite preliminary findings with us.

Reports given at various national and international symposia and conferences on cannabis have been carefully reviewed. There has been extensive discussion with researchers in other parts of the world so as to make maximal use of research that is being done abroad as well as within our own country. Reports from relevant government commissions both here and abroad have been reviewed for scientific content and their observations integrated with those of other scientific reports. In order to provide at least a partial picture of the diversity of overseas use patterns of cannabis an attempt has been made to bring together information on such use from a diversity of sources.

II. SUMMARY

SUMMARY

During the year since submission to the Congress of the first annual report on Marihuana and Health our knowledge of this complex issue has been significantly advanced in almost all aspects. We have a far better picture of the extent of present usage in the United States, of the basic nature of the material, and much of the essential basic research on short-term effects in animal and man has been done. Well controlled studies of more extensive human use in a laboratory setting are underway and two overseas studies of long-term, chronic users are nearing completion. Nevertheless even as the extent of the problem has grown so has our awareness of its complexity and of the difficulties of studying it.

In this summary of the second annual report we will attempt to describe the present state of our knowledge, to summarize the progress made in the past year and to again translate the disparate and necessarily technical data into as reasonable an answer as possible to the question: What are the health implications of marihuana use for the American people?

Despite the advances of the past year any simple answer to this disarmingly simple question is not likely to be possible now or in the near future. It is increasingly apparent that any satisfactory answer will have to take into account the many contexts of use, the purposes of use, the age, sex, physical, and psychological characteristics of the user, the material, its dosage and frequency of use, the route of use, etc. Even in assessing the immediate effects of marihuana on mental or physical performance it has become increasingly apparent that effects can vary greatly depending on the complexity of the task, the expectations of the user, the cultural context of use, user motivation, and the stage and level of intoxication of the user.

EXTENT AND PATTERNS OF USE AND ABUSE IN THE UNITED STATES

Much additional data has been gathered with respect to the extent of American marihuana use since last reporting. Nationwide studies of high school and college level youth have reported preliminary findings and there is now data on use in the general population and among employed groups. As use in the United States has increased, increasing sophistication is being shown in assessing such use. Researchers are going considerably beyond the oversimplified question, "Have you every used marihuana?" to inquire into the frequency of use, the level of use and the circumstances surrounding use. We are more confident that data is reported with reasonable consistency although more needs to be done to correlate reported use with actual use.

There is every indication that use has increased and is very widespread. In teenage and young adult groups use is very extensive - in some groups as high as 90% have used marihuana at some time. Even among young people, however, use is by no means evenly distributed in all areas of the country. For example, one national survey reveals that among persons 18-29 years old there are three times the percentage (over a third of the total age group) who"have used"in the West as compared with the other regions of the country sampled.

Among a still younger age group, the 12-17 year olds, a nationwide study has indicated that nearly one in four in the West has used the drug, a slightly lower percentage in the northeast and a bit more than one in ten "have used" in other parts of the country. It is noteworthy in all studies that where the percentage of those who "have ever used" is large, so too is the percentage who make regular use of marihuana.

Based on converging evidence from several recent surveys, we estimate the total number in the United States who have ever used marihuana to be 15 to 20 million. A very recently released National Commission on Marihuana and Drug Abuse survey has estimated that the total number at present may well exceed 24 million. Exact figures, of course, depend heavily on the date of the survey, the methodology employed and the underlying statistical assumptions which are made. Estimates may thus be expected to vary considerably from survey to survey depending on all these aspects. While many experiment and do not continue, over half are estimated to use the drug one or more times per month. About one in four of those who use that often do so three times a week or more. Since users fall heavily into the teenage, young adult group, we are talking principally about youth. It should be emphasized that even among youth, however, there is considerable variation from school to school. High school rates of having ever used range from as low as five percent to as high as 90%.

Last year it was noted that one norther California county that might be a bellwether of marihuana use more generally, had experienced a leveling off of drug use among high school students during the preceding year. The most recent annual survey of student use in this county now indicates sizable increases, especially in marihuana use, at all grade levels. About half "had used" at some time in the year. On the senior high level at the time of the survey (late spring, 1971) a third to a half of those who reported having used marihuana in the preceding school year had used it fifty or more times during the year. Even among junior high students in this high-use county, a third to a half of the users had done so ten or more times (from 13-29% had used at some point in the year).

Among college students 31 percent had reported having used marihuana by 1970. During 1971 this figure increased to 44 percent of the total college group. Even among four medical schools surveyed from one in six to seven out of ten students had tried marihuana with as many as nearly half in one school currently using.

Several studies suggest, not unexpectedly, that the more psychologically disturbed or socially unstable are more likely to make regular, heavy use of marihuana. School drop outs are more likely to be using marihuana as are those from disturbed families.

While the amount of data on minority group use is small, at least one study of Mexican-American youth in California suggests that among that group use was no higher than among high school youth in California generally.

Much remains to be learned about the relationship of drug use to vocational adjustment and job performance. One study conducted in New York State showed wide variation in the percentage of those in various occupations who had made use of marihuana one or more times per month. The range was from one in seven sales workers who had used to no reported use among the farmers sampled. Among regular users who actually used marihuana on the job, nearly half of those who had used and were employed in sales had smoked at work. About a fifth of those users in professional and managerial occupations had done so, but only 3% of those users employed in service and protective work had ever made use of marihuana in the work situation. There is no evidence in this study bearing on the issue of work effectiveness or industrial safety as related to drug use.

While heavier marihuana use is clearly associated with the use of other drugs as well - those who use it regularly are far more likely than nonusers to have experimented with other illicit drugs - there is no evidence that the drug itself "causes" such use. More frequent users are likely to find drug use appealing or to spend time with others who do so or in settings where other drugs are readily available. Marihuana use does not appear to have a causal role in the commission of crimes.

MARIHUANA USE IN OTHER COUNTRIES

Cannabis sativa, the plant from which all varieties of cannabis from marihuana to hashish are derived, grows and is used throughout much of the world. While use in the English-speaking countries and in Europe is typically recreational, much if not most of past and present use elsewhere has been as a work adjunct, to relieve fatigue, as a form of self medication, as part of folk medicine and in association with religious practices.

Almost all of the countries of Europe and North America have had a marked upsurge of interest in marihuana use - primarily among young people. Clear statistical evidence for this is frequently lacking but the surveys that have been done, the increasing amounts of confiscated material and the observations of those closely associated with youth, all appear to support this conclusion. Even countries, where use is endemic but where it has in the past been limited to certain segments of the population, have had a recent diffusion to university students and other previously non-using youth.

Generally our information about patterns of use abroad ranges from the results of carefully conducted surveys in a very few countries to a largely impressionistic picture. In only a few countries is it based on the observations of trained anthropologists. Much needs to be learned about use in other cultures and particularly about some of the social factors that serve to control its use. For example, in the one country in which use and sale is quite legal (Nepal), use of cannabis - especially its indiscriminate use - is apparently controlled by the conservative nature of the society and by parental and community disapproval. Even in this society, in which indigenous use is well controlled, there has been growing concern over the influx of young foreigners intent on more indiscriminate use.

In most countries in which cannabis use has had a long history it is at least nominally illegal; typically use is associated with the lowest classes and social opprobrium is frequently attached to use. In other countries in which cannabis has only recently been introduced, the official stance has varied from relatively permissive to highly punitive. The lack of adequate data coupled with the cultural diversity of the countries involved precludes any attempt to evaluate the general effectiveness of the various approaches to cannabis control cross-culturally.

THE MATERIAL AND ANALYTIC METHODOLOGY

Again it should be emphasized that what is termed marihuana varies greatly in potency from place to place and from time to time even in the same area. That which is sold in the United States is extremely variable ranging from psychoactively inert at the one extreme to hallucinogenic in large doses at the other. The type of marihuana generally available in the United States tends to be considerably less potent than that found in some South American countries and in other parts of the world. Adulteration, while reasonably common, is not usually done with more dangerous materials.

In the past year there has been a greater tendency for lay as well as scientific discussions to take into account such essential factors as potency, frequency of use and quantity in discussing marihuana effects. Nevertheless it should again be emphasized that awareness of these aspects as well as of user characteristics is basic to any thoughtful discussion of the drug and its implications.

While considerable progress has been made in the analysis and understanding of cannabis constituents, most of this is of primary interest to the technically trained. A great deal of work is being done in order to develop adequate methods for measuring the amount of cannabis constituents or their metabolites in human body fluids. Thus far a simple test analogous to the blood alcohol determination for marihuana intoxication has eluded us. Encouraging progress is being made, however, and it is hoped that such techniques will be forthcoming in the near future.

PRECLINICAL RESEARCH IN ANIMALS

Animal research, generally supported by limited clinical observation in humans, has clearly established that the margin of safety with cannabis and its synthetic psychoactive ingredient THC (delta-9-tetrahydrocannabinol) is very high. This work on the toxicology of the substances has laid the groundwork for the systematic study of more extended periods of carefully controlled administration in humans.

Work in animals has also shown that cannabis and its original constituents are rapidly transformed in the body into metabolites which are persistently present for several days. The implications of this persistence are unclear although it is possible that these metabolites may effect the later use of further amounts of cannabis or interact with other drugs taken in presently unknown ways. It may also be that it is the metabolites rather than the original drug constituents which are responsible for the drug's effects. Improved knowledge of the chemistry of these bio-transformation products may provide the key to a relatively simple test of the fact and level of marihuana intoxication. Persistence of these products may also permit detection of previous intoxication days after the initial event.

Studies of the distribution of the drug, radioactively labelled, have shown that its metabolites tend to concentrate in areas of the brain related to those functions effected by the drug. Despite this gross correspondence of drug concentration to brain function, much still remains to be learned about the specific mode of action of marihuana.

TOLERANCE

The issue of tolerance to cannabis has been an object of considerable discussion. By tolerance is meant a need which develops over a time, as a result of repeated use, for increasing quantities of a drug to produce a similar effect. Users have frequently reported that those who are experienced require smaller amounts of cannabis to achieve the same effect than do novices. This so-called "reverse tolerance" is an effect unlike that of most other drugs. Whether or not this reverse tolerance is based on metabolic and distribution changes after repeated use or it is the result of a learning process has not yet been determined.

Reports from countries where use is traditional suggest a level of use that would be highly unpleasant for the inexperienced user. This suggests that tolerance, at least for the effects which are perceived subjectively as unpleasant does develop. Whatever the subjective impressions of drug effects, it seems clear that experienced marihuana users can also tolerate larger doses in the sense that disruption of their performance on various intellectual, perceptual and psychomotor tasks is less than for the inexperienced.

In animals, for the most part, the evidence is clear that tolerance to certain effects of cannabis develops. It has been found in most species tested and is large. It is noteworthy, however, that in animals as well as humans tolerance may develop for some aspects of the drug's effects but not for others. Whatever the ultimate resolution of the tolerance question, it appears unlikely that in man a degree of tolerance comparable to that for opiates will be found.

EFFECTS IN MAN

Research of the past year has underscored the necessity of taking into account multiple aspects of the individual and the drug taking situation in evaluating marihuana's effects. These include such varied aspects as the characteristics of the material itself, the dose and route of administration, the individual's metabolic rate, his prior experience with the drug, his set (personal expectations) and the setting in which the drug is used.

While there is little doubt that the major psychoactive ingredient marihuana is delta-9-THC, there is still considerable uncertainty regarding the biological activity of the many other marihuana constituents. Of the two usual ways in which marihuana is consumed by man, smoking is by far the most common in the United States. As compared to eating the material, smoking results in considerably more rapid absorption with the onset of effects typically occuring within a few minutes. The quantity required for a given effect is significantly smaller when smoked and since the onset is rapid, the user can more readily control the drug's effects than if the drug is eaten. By contrast, when consumed orally it may require from a half to over two hours to feel the drug's effects which tend to peak later and to persist longer. In experimental studies with humans, it has become increasingly apparent that in the use of the synthetic THC the choice of the substance in which to administer the material orally makes a substantial difference in how rapidly and completely the THC itself is absorbed.

Experienced users appear to metabolize the drug more rapidly than do less experienced although the exact significance of this is unclear. It may partially explain the greater sensitivity or "reverse tolerance" that users have reported. Much remains to be done to clarify some of the implications of cannabis metabolism in man.

By now the acute effects of marihuana have been generally well elucidated. Subjective effects are highly variable partly depending on the user's expectations and the setting in which he consumes the drug. Experienced users report such subjective effects as: an awareness of subtlety of meaning in sight and sound and an increased vividness of such experiences. Frequently users report enhanced sensations of touch, taste and smell. Alteration of time perspective with an apparent slowing down of the time sense is almost universally reported. A sense of enhanced social awareness is often reported with low dosages, but at higher levels this is apparently diminished and there may be social withdrawal. Although emotional reactions reported by regular users are usually pleasant, one in five experienced users in one study reported having at times experienced temporarily overwhelming negative feelings.

Several studies have underscored the critical role of attitude and expectation in determining effects at least at low to moderate dosage levels. Such expectations can result in the individual having subjective reactions to an inactive material that are similar or identical to the active drug.

The two most consistent physiological effects of marihuana continue to be an increase in pulse rate and a characteristic reddening of the eyes. The latter occurs even with oral dosages indicating that it is not primarily the result of smoke irritation. Recently, it has been found that marihuana use decreases intraocular pressure, a finding that may have therapeutic implications in glaucoma patients.

Although marihuana users frequently report substantially increased hunger at the time of use, there is no evidence that marihuana lowers blood sugar. It may be that the effects on appetite are an indirect result of an enhancement of the subjective sense of taste leading in some to increased food consumption.

Neurological correlates of marihuana use seem minimal although it is possible that marihuana-induced drowsiness may obscure small drug-related effects on the electroencephalograph. There is some EEG evidence that tends to objectively confirm the report of users that they have an enhanced ability to ignore outside stimuli while high.

Effects on Intellectual and Psychomotor Performance

More recent findings continue to confirm earlier reported observations that acute marihuana intoxication causes a deterioration in intellectual and psychomotor performance which is heavily dose-related as well as dependent on the complexity of the task. The more complex and demanding the task, the greater is the deterioration in performance. When alcohol and marihuana are consumed together the decrement in performance is greater than when either is used alone. To some degree at least, experienced users seem better able to compensate for part of the effect of marihuana than do inexperienced users.

Marihuana clearly has an acute effect on short term memory which has now been confirmed by many investigators. One explanation for this impairment is that the drug reduces the ability to concentrate while intoxicated, preventing the implicit rehearsal that may be essential to remembering newly acquired information.

Driver Performance

Driver performance has been of considerable research interest and such research is continuing. There is, however, increased reason for believing a motorist's performance is significantly impaired by marihuana intoxication.

Although initial research suggested relatively slight impairment of performance on a driver simulator, more recent work suggests that this may not be the case. An increase in time required for braking has been reported as has a marked increase in glare recovery time which persists for several hours following intoxication. Research on driving tasks more closely resembling actual driving conditions is going on to more accurately specify the degree of impairment likely under varying conditions. It should be noted that the performance of a highly motivated test subject under laboratory conditions may be considerably less impaired than that of a driver functioning under more typical driving conditions. Under usual driving circumstances multiple distractions are common and the driver may be less motivated. The possibility of a spontaneous recurrence of an earlier drug experience (a so-called "flashback"), related to the use of marihuana and other hallucinogens and which interfered with driving, has been raised by some case reports. Evidence for the frequency of such phenomena in this or other contexts is generally lacking.

Acute Physical Toxicity

Death from an overdose of cannabis is apparently extremely rare and difficult to confirm. This is consistent with animal data which indicates the margin of safety with cannabis or its synthetic equivalents is quite high. Nausea, dizziness and a heavy drugged feeling has been reported usually as a result of an inadvertent overdose. There have, however, been a number of cases of acute collapse following an attempt to intravenously inject marihuana or some preparation made from it. It is not clear whether these were the result of an acute overdose of cannabis constituents *per se* or a combination of other factors related to the injection process. In view of the hazards such intravenous use seems especially dangerous. While there has been one case report of epileptic seizures temporally related to marihuana use, there have been other past reports of the efficacy of cannabis as an anti-seizure medication in children. In general, it appears that acute toxic physical reactions to marihuana are relatively rare.

Chronic Physical Effects

Frequent, relatively heavy use of cannabis is still rather uncommon in the United States. Thus, observations on the implications of such use are derived from cultures very different from our own. The marked differences in diet, living standards including level of medical care and in patterns of use make it difficult to apply overseas observations to our own domestic situation. Nevertheless, such observations may provide valuable clues to the possible implications of American use and when combined with the results of other research may be quite valuable.

While respiratory complaints have long been reported as a result of cannabis use, it is not always certain to what degree this is the result of the drug or the tobacco with which it is frequently mixed. Among as American military sample of heavy hashish smokers complaints of bronchitis, asthma, and nose and throat inflammation were common and reported to improve upon discontinuing the drug. While there have been reports of impaired liver function as well, upon closer examination these seemed to be more closely related to alcohol use than to cannabis use.

Blood circulatory difficulties in the legs have been reported in a North African sample of users as have arterial changes among some young multiple drug users in the United States, but the role of cannabis in these is still unclear.

There has also been a report of slurred speech, staggering gait, hand tremors and difficulties in depth perception in a few adolescent patients, but the exact significance is difficult to evaluate since these patients were also using other drugs.

One of the most serious reports is a recent one based on some very recent British work which, using radiographic techniques, found evidence of cerebral atrophy in ten young cannabis smokers. However, some researchers have questioned whether such techniques can be used to demonstrate cerebral atrophy. Unfortunately the subjects were multiple drug users, with 8 out of 10 admitting to the use of amphetamines, a drug which some reports have implicated in organic brain changes. The comparison group was not altogether appropriate and thus the role of cannabis remains uncertain. Because of the seriousness of the finding, however, this work will be followed up by careful animal research as well as further clinical studies to explore this serious possibility. The authors themselves caution against overinterpretation of their work and emphasize the need for additional research.

Preliminary findings of a study of 31 male chronic hashish users in Greece and of a similarly sized Jamaican sample of intensively studied cannabis users are noteworthy for the relative absence of pathology in these chronic using groups. It should, however, be emphasized that the samples are small and the data are preliminary. Given the small size of the samples, rarer or less obvious consequences of use may be missed. Larger scale epidemiological studies of chronic users are planned to overcome the limitations of smaller pilot efforts.

Genetics and Birth Defects

Among the most serious consequences that might ensue from the use of any drug are persistent changes in the genetic heritage of users or the production of birth anomalies as a result of drug use by parents. The amount of evidence bearing on this question is modest. What work has been done has found little evidence of chromosomal abnormalities in marihuana users as compared to matching nonuser controls. With respect to birth defects that might be the result of maternal cannabis use during pregnancy, there have been several case reports but it is impossible to be certain whether there is a differential rate of such defects between users and nonusers. It is known that in animals THC can cross the placental barrier and enter fetal circulation. Once again it must be emphasized that the potential seriousness of the effect makes the use of marihuana (or other drugs) of unknown potential for producing birth defects unwise. This is especially true for women during their reproductive years.

Cannabis and Psychiatric Illness

Any discussion of the relationship of cannabis use to psychiatric illness must take into account the formidable difficulties of establishing the role of any drug as a causal factor in mental illness. It is typically extremely difficult to separate out the role of the drug from the many other factors that may play a role in the etiology of a specific disorder. In addition, in those countries in which chronic cannabis use is common, epidemiological surveys are virtually nonexistent and adequate diagnostic evaluation is more often the exception than the rule. As a result, the diagnosis of cannabis psychosis may be used as a catchall description for all those with a known history of cannabis use who are also emotionally disturbed. Finally, we are aware that non-drug factors such as the pre-existing psychological state of the user and the circumstances surrounding use can be of fundamental importance in determining the user's response to the drug.

Cannabis psychosis has been used as a diagnosis for many years in countries in which cannabis use is traditional. During the nineteenth century it was popularly believed in India that marihuana produced mental illness. The Indian Hemp Commission, upon learning that such a diagnosis was frequently based on the impressions of laymen, did a careful analysis of its own and concluded that drug use was a factor in no more than between seven and thirteen percent of admissions to Indian mental hospitals. In other countries estimates of the percentage of admissions that are cannabis-related range from 2-3% in South Africa to as high as 17% in Morocco. In most reports it is simply impossible to distinguish between illness resulting primarily from toxic effects of cannabis and an aggravation of a previously existing serious mental disturbance.

Diagnosis is typically most heavily based on a history of drug use although attempts have been made to take into consideration the duration of the illness and its failure to develop into a long lasting schizophrenic picture. Symptoms which have been emphasized in the Eastern literature have included: acute or subacute onset of confusion, visual and auditory hallucinations and paranoid ideation sometimes accompanied by agitation and aggression.

In the 1930's toxic psychoses were reported among some marihuana users who were described as recovering in a few days. During the experimental phase of the investigation conducted by the La Guardia Commission, psychotic episodes were reported by one in nine of the 77 subjects studied. Beginning in the late 1960's there has been a spate of reports of adverse psychological consequences of use in the United States. Unfortunately, few of these provide any indication of how frequently such reactions occur in a large population of users. A wide range of symptoms have been reported, most more nearly resembling a panic state than full-blown mental illness. There is, however, little question that given a sufficiently high dose, hallucinations and delusions can occur. While such adverse psychological reactions are more common with the inexperienced and when inadvertently high doses are ingested, they occasionally occur even with low doses. Reports typically are of individuals who have sought treatment for their difficulties and it is usually difficult to be sure how much of the pathology displayed is the result of previously existing personality problems rather than "caused" by marihuana use. There is some evidence that when a sample of frequent marihuana users is matched with their non-using friends, the amount of psychiatric symptomatology found in both groups is greater than in youth generally. This suggests that heavy marihuana users may be drawn from a population with an above average amount of pre-existing psychopathology. Thus, use, especially in association with other drugs, may more typically aggravate already existing psychiatric problems rather than in itself causing such illness.

There have been a number of reports on adverse psychiatric reactions to marihuana use in Vietnam among American troops. Onset was usually acute and again, the reports suggest that pre-existing pathology is an important non-drug factor. Almost certainly many of those most attracted to drug use are individuals who have personality problems. In some cases the drug is sought with a conscious hope that it will be psychotherapeutic.

While marihuana use has been widely described in the Eastern literature and to some extent more recently in the West as resulting in a loss of motivation, the question of its role in the process is still unresolved. Many of those most attracted to its use are "amotivated" by conventional standards. The time and effort required to obtain drug supplies and use them may also further erode the expression of more conventional motivation. There is also the definite possibility that the drug and the personality of the user interact in such a way to further intensify the loss of conventional motivation.

THERAPEUTIC USES OF CANNABIS

While use of cannabis is not a medically accepted mode of treatment for any illness in the United States today, the drug has had an ancient tradition of medical use. Even today in much of the world where Western medical practice has made only modest inroads, cannabis retains an important role in self-medication and in folk or native medicine. The range of diseases and other medical conditions for which it has been and continues to be used is very long. For much of the nineteenth century and well into the twentieth, cannabis was a recognized part of the physician's armamentarium against illness although its lack of water solubility and its variable potency were problems. Gradually it was supplanted in Western medicine by drugs that were more consistent in their effects or more conveniently used. Since most of the early reports of use were clinical case reports rather than drug tests conducted under carefully controlled conditions, the relevance of this older literature to potential modern use is questionable.

During the early 1940's the development of "Synhexyl," a chemically related drug to marihuana, generated some interest in medical uses. Some attempts were made to use it in the treatment of depression, the treatment of alcoholism and in preventing epileptic seizures. Results of these limited studies were reported to be generally favorable. Some later research demonstrated that cannabis preparations had an antibacterial action in the treatment of dermatological conditions as well as in the treatment of otitis and sinusitis.

More recently with the increase in illicit use and the development of a synthetic form of THC, there has been a revival of interest in potential therapeutic uses. In addition to the experimental uses reported in last year's report, there has been a continued interest in the drug's possible therapeutic value in the treatment of depression and in the possible development of an antihypertensive agent. Most recently it has been found that marihuana reduces intraocular pressure. This observation holds forth the promise that cannabis or some chemically related synthetic may prove useful in the treatment of glaucoma. With the greatly expanded research effort into marihuana and related synthetic materials, there is a strong possibility that cannabis derivatives, very possibly in chemically modified form, will once again achieve medical acceptance in the treatment of a variety of conditions.

FUTURE RESEARCH DIRECTIONS

As our knowledge of the properties of marihuana and related materials has expanded so has our awareness of the many questions that require answers in assessing the health implications of their use. The overall question of what dosages, frequency and duration of use are clearly likely to be injurious to health in various groups remains unresolved.

Because the material in its natural state is quite variable, more needs to be learned about it since the implications of use for different types of marihuana may not be the same. The mode of action of the drug and its many components needs to be elucidated. Little, for example, is presently known about the effects of marihuana on the biochemistry of the brain.

The whole question of interaction between marihuana use and that of other drugs is an important one. Some of the reports of adverse effects may be the consequence of multiple drug use in which one or more other psychoactive drugs in combination with cannabis are more injurious in combination than alone.

The recent report of brain atrophy possibly related to marihuana use needs to be carefully followed up in animals and further clinical studies. Adequate assessment of the psychiatric risks of use require that we do better epidemiological studies to determine the incidence of the adverse consequences that have been reported to date. It would be especially valuable to know the extent to which such adverse consequences occur in those without evident pre-existing psychopathology.

The limitations of relatively small scale, intensive studies of chronic users require that we do more extensive studies of larger populations in order to determine what, if any, are implications of use that may otherwise go undetected. We know, for example, that some of the most serious effects of other drugs (e.g. tobacco and birth control pills) in widespread use would not have been determined but for larger scale study of their use.

Present longitudinal studies of American users should be expanded to determine the longer term implications of use that may not be evident over a shorter time span. Although there is some reason to suspect that many young people, for example, modify their patterns and level of use of marihuana over time, we know little about the factors that influence changes or what changes typically occur.

While we know something about the social conditions of use much more should be learned about the social reinforcements of use - i.e. what are the factors in the user's relationship to others that tend to foster beginning use and to perpetuate various patterns of use.

More needs to be learned about the implications of use for such areas as the operation of motor vehicles, traffic accidents and industrial safety and performance. The economic implications of use should also be explored.

Studies of cultures other than our own may be useful in improving our social means of control not only of marihuana but of other drugs as well.

The extent of need for and the most effective means of treatment for the heavy user of cannabis needs to be explored, since it is evident that with a general increase in the numbers who have ever used has also come a significant expansion in the number who use extensively.

Finally, preliminary indications of possible therapeutic implications for the use of cannabis or its derivatives require careful exploration.

III. EXTENT, PATTERNS, AND SOCIAL CONTEXT OF USE IN THE UNITED STATES

Our knowledge of the extent of marihuana use has improved considerably since the initial Marihuana and Health Report to Congress in 1971. Although many separate studies had been conducted by early 1971, none looked at the non-student or general population and only sketchy figures were available for the nation as a whole. Since then, several studies of the general population have been reported, both in selected areas and nationwide. Two nationwide studies of students (high school and college) reported preliminary findings. One community continues to survey high school students' drug use in successive years, providing at least a limited view of possible shifts in interest over time among young people.

The Context of Assessment

The question of how to define marihuana abuse is still difficult. The term abuse has had a variety of meanings, ranging from any use of the substance to only that having clearly detrimental effects. In the present report, use is reported as such without judging whether or not all or some of the users might be considered "abusers."

Most studies used for this report have not separated accounts of marihuana use from hashish use, nor differentiated smoking from other possible routes of administration. Thus, all cannabis products might be included under the term "marihuana", and the fact of this inclusiveness may or may not be acknowledged.

The various levels and gradations of use, in terms of frequency, regularity, and recency, are now more often being reported routinely.

This is an improvement over past assessment that relied mainly on gross reporting of those who had used marihuana one or more times. It is of interest that conceptions of user types have come in some eyes to be characterized by more use of marihuana than formerly reported. In one study, "experimenters" were those who used it one to ten times, "occasional users" ten to fifty times, and "frequent users" fifty or more times (10). In another study, the authors decided not to characterize as users any who used marihuana less often than once a month (11). Undoubtedly, such conceptions will continue to change as the extent and patterns of use change.

Two other features of the reporting problem should be mentioned again. One is the question of the reliability and validity of data on illegal drug use. Another is the degree to which researchers can furnish guarantees to subjects on the confidentiality of data.

Quality of the Data

Little or no work has been done to establish the validity of questionnaire data on illegal drug use -- that is, to correlate respondents questionnaire responses and their actual drug use. Some work has, however, been done on the reliability of questionnaire responses by teenagers in classroom settings (10). In this research based on a carefully developed drug usage questionnaire, students responded nearly identically two weeks later on re-test regardless of whether or not they provided their names. This finding suggests that reasonable assurances of anonymity are adequate to reassure teenage respondents of the sincerity of the research aims. More such work needs to be done to assess the adequacy of survey data as an indicator of actual drug use in various populations.

Researchers' Immunity from Prosecution

Federal law will protect researchers from being forced to divulge certain kinds of information provided in drug studies (PL 91-513), and procedures for obtaining this immunity are being developed.
Also, state laws vary in this respect, so researchers must consider their legal status with regard to possible pressures to reveal data and individuals' responses.

Estimates of Cannabis Use

The most recently reported nationwide survey of marihuana users in the general population was done as part of a more general study of psychotherapeutic drug use, mainly of the legally prescribed drugs (20). The following percentages based on a survey conducted in 1970-71 were calculated for the 18-29 age group* in four regions of the country:

Extent of Marihuana Use Nationwide, 1970-71, Persons Age 18-29*

Region	Currently using during last two months	Ever used	No. times used			No. surveyed
			1-4	5-49	50 or more	
	%	%	%	%	%	
Northeast	4	12	5	5	2	182
North Central	5	11	7	1	3	168
South	2	12	8	3	2	396
West	17	37	10	10	16	101

Parry, Cisin and Balter, 1971

*This group has been found in earlier studies to include the largest concentrations of marihuana users.

According to the authors, these estimates are conservative. Although the numbers surveyed in each region were relatively few and therefore have a fairly high associated sampling error, there is consistency with similar surveys made of separate locales in one of the regions, the West. In 1968-69, the same age group was studied in San Francisco and in 1969 residents of a nearby suburb were also asked about their marihuana use (7). Figures are available for comparing the three surveys:

	Percent Who Ever Used Marihuana
San Francisco, 1968-69	32
Contra Costa, Calif., 1969	35
West (entire region), 1970-71	37

Since marihuana use rates have increased generally over the past several years, it is plausible that the Western region could well have a marihuana use rate of 37 per cent in 1970 - 1971. It is interesting to observe that few differences appeared among the rates for the Northeast, North Central area and the South, whereas earlier surveys had indicated lower rates in the Midwest and South. (It should be noted, though, that frequency of use was generally lower in the North Central area and the South than in the other two regions.) Statistics tabulated by region may sometimes reflect different combinations of states, and the inclusion or exclusion of certain states can strongly affect one region's rate. There is a strong possibility, however, that earlier differences among regions have actually diminished with more widespread use of marihuana.

A second nationwide interview survey was conducted in May, 1971, on a younger adolescent group, age 12-17 (12). Surprisingly, the proportion of that group who had ever used marihuana was as high or higher than that of the 18-29 year group. (Having conducted the survey a few months later than the 18-29 year old survey could have resulted in a slight increase, but probably not a significantly larger one.) In a nation as a whole, a national household survey of 498 youngsters revealed that 15 percent had tried marihuana, and 3 percent reported having used it 60 or more times. Broken down by region, the proportions were:

12-17 year group in regions	Ever used marihuana
Northeast	20%
North Central	13%
South	11%
West	23%

(Josephson, et al., 1971)

According to the authors, the teenagers in the South who had used marihuana were mainly experimenters; in the group in the West, however, 7 percent were frequent users (60 or more times).

The use rate among 12-17 year olds rises rapidly with age. A breakdown by age of those who never tried marihuana and were not interested, never tried but were interested; had experimented, used occasionally, or used frequently.

Extent, Interest, and Frequency of Marihuana Use Nationwide, 1971
Persons Age 12-17*

Age:	Non-users, not interested in trying	Non-users, interested in trying	Experimenters (1-9 times)	Occasional users (9-59 times)	Frequent users (60 or more times)
12-13 years %	87	10	3	**	0
14-15 years %	74	11	11	3	1
16-17 years %	64	8	14	5	9

* Josephson, et al., 1971
**Less than 1%

In the span from 12 to 14 years, the rate increased strongly, suggesting that introduction often begins at the junior high school level. It rose sharply through the 17th year, to a rate as high as that for the older age group, 18-29. It appears that senior high schools and colleges now enroll a large minority of students who are already familiar with marihuana based on their earlier use.

All polls in the past have shown that users are most heavily concentrated in the young adult age group. Thus, the regional figures above should be considered the highest rates that could be found in any age group. Figures from New York State's general population in 1970 suggest that in some areas the rate for all persons over 14 years of age may approach the size of the regional rate for young adults (5). Over seven thousand respondents in a New York State study were interviewed in 1970 on their use of legal and illegal drugs. The following breakdown of use was reported:

New York State Residents' Use of Marihuana, 1970*

	%	
Regular users	3.5	10.5% ever used
Infrequent users (fewer than 6 times/mo.)	4.0	
Former users (no use in last 6 months)	3.0	
Never used	87.7	
No data	1.9	
	100.0	
Total number surveyed	7500	

*Chambers, May, 1971

Thus, over 10% of all New York State residents over 14 years of age had used marihuana at least once. This can be contrasted with 12% of 18-29 year olds in the Northeast region who ever used marihuana.(20)

Using all available recent figures, McGlothlin has estimated the following rates of marihuana use for mid-1971: (17)

Estimate of Marihuana Use Nationwide, Mid-1971*

	Ever Used
Overall (nationwide), age 11 and older:	9%
18-24 years (non-student)	22%
25-34 years (non-student)	10%
35 years and older (non-student)	2%
Students grades 6-8	6%
Students grades 9-12	22%
College students	42%

*McGlothlin, 1971

According to these estimates, college students as a subgroup of the 18-24 year population group have a usage rate about twice that of the non-student age group. And high school students have a rate equal to that of the 18-24 year non-student age group.

McGlothlin estimated that the number of persons who have ever used marihuana in the country as of mid-1971 was about 15 million, or 9 percent of the population 11 years of age or older. This estimate is useful because it provides a "ballpark figure" for an evaluation of usage. It is drawn from a number of separate studies which reached essentially the same conclusions and thus has a degree of reliability. However, the true rate in the population may vary from the gross rate of 9 percent because of sampling error. Projecting the trend of marihuana usage into early 1972, we estimate that it probably falls between 15 and 20 million.

On January 21, 1972 the National Commission on Marihuana and Drug Abuse released its findings which indicated that the number of Americans who have ever used marihuana is 24,600,000. Of this group the Commission estimates that 8,340,000 are current users. Differences of this nature are understandable and can be attributed to the methods of conducting the studies on which the estimates were based. Further analyses and studies over the next year will clarify and refine these estimates.

Among all those who have ever used marihuana, McGlothlin estimated the following levels of use: (17)

3% using daily
11% using 3-6 times a week
40% using 1-8 times a month
46% stopped using or used less than 10 times

Thus, a third to half of those who ever used marihuana appear to have stopped or to use it very infrequently. A small proportion of all current users - about 5% - appear to be regular daily users.

McGlothlin also estimated the use rate of hashish as a percentage of use of all cannabis products to be 7%. He estimated also that daily marihuana users consume about 3 cigarettes per occasion, and for a 3-cigarette-a-day user, about 15 mg. of THC daily.

Student Rates and Changes Since 1970

Since the beginning of an increase in marihuana use in the mid-1960's, studies of students have predominated in the available research, but such are mainly of separate schools or campuses. The nationwide survey of 12-17 year olds reported above is the first that can be used to estimate high school students' use generally, although it is not a perfect indicator of students' use (12). According to the authors, the survey sample did not include as many black youngsters or those from families with low education as are found in the general population. (Further study of these and other population sub-groups is needed.)

Separate studies of local schools often produce rates that vary widely from the national rate described above. Among the separate studies of high schools reported [illegible] 1971, for example, the rates ranged from 5 to 90% (2).

One school system, in Northern California, has been looking at its drug usage rates every year since 1968 (4). The proportion of senior high students in 1971 who used marihuana at least once in the preceding year ranged from 41 to 59 per cent (the lower range more typical of girls) and the proportion of junior high students, from 13 to 29 per cent. The senior high rates were considerably higher than the 12-17-year-olds rates for the West and the national figure for a comparable age group. (See tables above). Moreover, the comparison is between proportions in this county who "used in the past year" and 12-17 year olds nationwide who have "ever used" marihuana. Of greater interest is the comparison of 1970 and 1971 figures, and a review of the perceptible slowing of the rates that appeared in 1970.

In the county-wide school survey, considerably more students used marihuana in 1971 than in 1970. The percentage increase over 1970 among senior high students was as great as the increase between 1968 and 1969. Among junior high students, increases were also substantial. The changes were much greater than those between 1969 and 1970, when it was thought that use might be leveling off or even declining (especially on the junior high school level). Rates of use of other drugs increased in 1971 also, but not as much as did those for marihuana.

Not all the increases in San Mateo were in the "experimenter" category. Sizable increases also occurred in those who had used ten or more times, or 50 or more times. On the senior high level a third to a half of those who reported having used marihuana that year used it 50 or more times. Among junior high students, from a third to half of the users had done so ten or more times during the school year (the category of 50 times or more was not reported separately). In senior high school, heavier users of marihuana were almost as numerous as heavier users of alcohol and tobacco at all four grade levels, reaching 30-35 percent at the senior grade level.

Nationwide marihuana use rates for college students have been measured for two years consecutively and they too show a large increase (23, 9). The 31 percent of students who reported ever having used marihuana in 1970 had increased to 44 percent in 1971.* The figure of 13.6 percent for those who used marihuana at least every week or two in 1970 had increased to 21.6 percent in 1971. There are also nationwide figures for hashish use by those students in 1970 and 1971:

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*This figure approximates the one of 42% estimated by McGlothlin for college students in mid-1971 (17). The difference of 2 percentage points is within the limits of sampling error for surveys of the size made.

	1970	1971
College students' use of hashish at least every week or two*	7.3%	9.6%

(*Rossi, 1971)

Hashish users appeared about half as frequently as regular marihuana users, a surprisingly high rate. In the Rossi study, all drug use increased among college students from 1970 to 1971, but the rates for use of marihuana and psychedelics showed the greatest incrases. About half as many students use marihuana now as use tobacco.

Again, individual campuses varied in their use rates. Of those 1970-71 studies that came to our attention, the percent of students who had ever used marihuana varied from a low of 23% to a high of 78% (2, 18).

Medical schools are of particular interest in examining marihuana usage figures because medical students are usually seen as more serious and less alienated than undergraduate students. A 1970 study of four medical schools in different areas of the country showed that the rates vary as widely and are as high as rates in other schools (15). Among the four schools, from 16 to 70 percent of the students used marihuana at least once, and from 6 to 44 percent were using it currently. The school itself was the most important factor in predicting use, according to the authors. That is, although individual student characteristics were related to marihuana use, characteristics of institutions and campus cultures were even more closely related.

Marihuana Use in Other Groups

Drug use, including marihuana use, has been studied in a number of groups other than students. In the 1971 Marihuana and Health report, findings were cited for employed youths, high school dropouts, "hippies", Negro men in St. Louis, and servicemen. More recent findings are available on some of these same groups, but studies of certain other groups of interest or concern have not been conducted or reported. Some of these are: Spanish-speaking youth, American Indian youth, white ethnic youth, and young college graduates as employees or parents.

Although the hippie movement has diminished in intensity, smaller numbers of hippies continue to live in such traditional areas as San Francisco's Haight Ashbury section and New York's East Village. And although the opiates and so-called dangerous drugs (amphetamines and barbiturates) appear to have supplanted the hallucinogens in those areas, marihuana continues to be the most-liked drug, used by a larger proportion than any other. Two studies begun when hippies were more numerous and newsworthy have now been completed and they provide considerable detail on the background and on drug-taking practices of this group (11,13).

Within the drug-using California group studied, intemperate users were less common among those of middle class origins, moderate political background and those who had moderately good communication with their parents (13). As in other studies, school dropouts, and those from disrupted families tended to use drugs most heavily.

In a study comparing New York hippies, so called weekend hippies, and non-hippie drug users and non-users, 14 to 35 years of age, daily marihuana use was most common among those defined as hippies (from one fourth to one third of the group studied (11). But one third of the non-hippie users were also using marihuana on at least a weekly basis. Hashish was being used at the time of the study by 70 to 80 percent of hippies; about 10 percent had used it but were not using it currently. Almost half of the non-hippie user group was using hashish currently, and about a fourth had used it formerly but were not at the time of the study. The male hippies and weekend hippies tended to be from a somewhat lower socio-economic background than the female hippies and the non-hippie drug users. According to the authors, the hippie life may have been a flight from modest circumstances for males, but for females perhaps a flight from affluence. The parental families of hippies, especially those of the females, tended to be more unstable and disrupted than others. In addition, far more hippies were dropouts from high school and college than were the non-hippie users.

Another indication of the relationship of school attendance to drug-taking was seen in the Columbia University study of teenage drug surveys (10). Twice as many of those who were absent in the first stage of the study reported drug use in a later stage as compared with those students who were initially present. The incidence of heavier drug use among absentees was triple that of attending students. In another report, a distinct phenomenon of "hooky parties" was observed in Harlem. Some youngsters occasionally spent the entire day away from school in an unsupervised home experimenting with drugs and sex (14). Marihuana was the primary "high", sometimes taken in combination with amphetamines, barbiturates, or wine.

Ghetto youth have in past years been considered highly susceptible to drug use of all kinds, including marihuana. Although few studies have been conducted of low-income youth of any race or nationality, recent findings tend to indicate that marihuana use may be no prevalent among minority youth than amont the majority. A description of black and Mexican-American ghetto youth age 16-22 years in a California work training program (1967) showed that 54% had used marihuana at least once (16). This figure is no higher than that found for California boys in senior high or college at that time. A study of marihuana use in Houston, Texas, high schools showed that drug use rates were highest for "Anglos", next highest for Chicanos, and lowest for black and other students (21).

A recent summary of data on extent of marihuana use by U.S. servicemen in Vietnam suggest the following trends: (8)

1. The percentage who have "ever used" has been increasing over the past two years (at least) and now may be considerably more than 50 percent of lower grade enlisted men. (A 1970 study found that 68 percent of a group of airborne soldiers had used marihuana at least once in Vietnam.)
2. About half of those who try marihuana continue to use it occasionally or regularly.
3. There is a marked tendency for greater incidence of use in the lower ranks; few officers and higher ranking enlisted men are found in the user category.

Finally, use of marihuana by persons in different occupational groups, as individuals, and while on the job, is of interest and concern. A secondary analysis of data from the general population of New York State showed that occupational groups do show some variation, from a high of 9 percent regular users among sales workers to a low of 0 percent among farmers.* The variation in levels of use for seven occupation groups and two categories of unemployed is seen below:

Use of Marihuana*

Occupational group:		Regular users (at least 6 times per mo.)	Infrequent users (1-5 times per mo.)	Former users (No use in 6 mo.)	Never used	No data
Professional, technical workers, managers and owners	%	3	4	4	87	3
Clinical and other white collar workers	%	4	5	4	86	2
Skilled and semi-skilled workers	%	4	5	5	84	2
Unskilled workers	%	5	6	4	83	2
Service and protective workers	%	4	3	3	89	1
Sales workers	%	9	4	1	85	1
Farmers	%	-	2	-	98	-
Not employed housewives	%	**	1	1	96	2
Other not employed	%	6	6	4	84	1

*Chambers, July 1971
**Less than .5%
***To compare with other studies on the "ever used" basis, subtract "never used" plus "no data" from 100%

The occupational differences may be partly an artifact of age differences among those groups. The category of "other not employed" undoubtedly includes most of the student population. Of even greater interest are the results of a question put to each employed drug user about his or her use of illegal drugs on the job. (Of all illegal drugs, marihuana was the one most frequently used on the job.) Rather large proportions of regular users in some of the groups reported that they used marihuana while working, specifically sales, clerical, and unskilled workers. The proportions for seven occupational groups are seen below. (Note that the figures below are percents based on users and represent even smaller proportions of the complete occupational groups.)

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*It is not known whether these differences are statistically significant.

Regular Users' Use of Marihuana on the Job*

Occupational groups:	Percent of regular users who reported any use of marihuana on the job %
Professional, technical managers and owners	21
Clerical	35
Skilled & semi-skilled	22
Unskilled	35
Service & protective	3
Sales	44
Farmers	(no regular drug use)

*Chambers, July 1971

Although the figures above represent a fairly small proportion of the employed population of New York State (about 1% of employed persons in 1970), the number who reported such use on the job is not insignificant (about 78,000). It is these kinds of data that should be collected more widely and continuously if the effect of marihuana use on daily life is to be realistically assessed.

Individual Histories of Marihuana Use

The spread of marihuana use has been so recent that there is as yet no good summary of histories of individual usage. There is some evidence that cannabis is likely to be used for long periods, sometimes over a lifetime (17). According to McGlothlin, the marihuana using population in the U.S. today contains more infrequent users than might be expected, because of their recent introduction to the substance (17).

Survey data collected from students are imperfect as indicators of individuals' past and future use, but do provide some hints about such patterns. Among students in one large study, moderate-to-heavy drug users were much more likely to plan to smoke marihuana in the future than were casual or experimental drug users. Seventy one percent of the moderate-to-heavy users reported such intentions, compared with 29 percent and 10 percent of the less frequent users (1). A recent study of matched groups of heavy and casual smokers also reported this same general tendency (19).

Marihuana and the Use of Other Drugs

Little new evidence has appeared to illuminate our limited insights into marihuana's relation to other drug use. In the earlier report, the following facts and hypotheses were mentioned: 1. Most "hard" drug users have used marihuana previously, but most marihuana users do not progress automatically to heroin; 2. Marihuana use is usually preceded by experimentation with alcohol and tobacco; 3. Marihuana use is related statistically to the use of most other drugs (including alcohol and tobacco), but the major temporal patterns have not been carefully studied; 4. Frequency of use of marihuana is even more closely related to the use of other drugs than is mere incidence of use. The more frequently a person smokes, the more likely he is to use other drugs; 5. Heavy marihuana use apparently tends to involve the user in a drug-oriented group or subculture which may alter his life style and his conception of himself. It may also increase his opportunities to try other drugs, including opiates; 6. There apparently is an individual "drug proneness" factor that accounts in part for the phenomena of progression, substitution, and multiple drug use.

A recent nationwide survey of teenage marihuana use confirms even more strongly the statistical association of marihuana use with other drugs (12). In the case of the use of "downs", for example, only 1 percent of non-users of marihuana had ever tried "downs", while 18 percent of marihuana experimenters and 71 percent of occasional or frequent marihuana users had tried them. Such an association does not, of course, imply that marihuana use "causes" the use of other drugs.

Some new findings suggest further hypotheses worth testing in depth and with a variety of populations. They are: 1. Marihuana use is more prevalent among those who obtained a normally prescribed psychotherapeutic drug from a friend, spouse or relative, without a prescription, than among those who obtained the same kind of drug from a physician (7). This finding suggests that a certain kind of attitude toward all drug-taking may be typical of those who use illegal drugs; 2. Teenage marihuana users are more likely to use other drugs than are non-users, with the exception of cough syrup and glue (24). It is possible that young glue and syrup users may be drawn from different socio-economic groups and thus follow different patterns of drug use; 3. In contrast to hippies (both full-time and "weekend" hippies), most non-hippie drug users in New York apparently used marihuana for at least three years (the period of the study) without going on to other drugs (11). The hippies tended more often to smoke tobacco cigarettes than did non-hippie drug users, but tended less often to drink alcohol. These findings suggest, as did another finding about West Coast hippies, that alcohol use may be replaced by use of illegal drugs among the heaviest drug users, and merely provides variety in psychoactive substances among more moderate drug users.

Socio-demographic Characteristics of Users

The socio-demographic correlates of marihuana use were fairly consistent in the U.S. student studies examined in 1971. In most studies, marihuana users tended more often to be male, young, single, middle or upper-middle class* and not participating in formal religion. At least one aspect of this picture may be changing. The ratio of males to females appears to be lower than in former years. As a general rule, the ratio has been estimated at about 3 males to 2 females among students and 2-to-1 in the rest of the population. In a recent survey of the adult population in San Francisco and a nearby suburb, the sex difference was not present at all in the 18-to-34 year old group (7). It was still apparent, however, in another West Coast study of high school students, both in prevalence (those who had ever used) and frequency of use (4).

The Sociology of Marihuana Use

It is well recognized that marihuana use, like much other illegal drug use, occurs first in a social group, is supported by group norms, and functions as a shared social symbol. In the case of marihuana, some of the drug effects themselves appear to occur only when learned in the presence of others. As marihuana use comes increasingly under the scrutiny of social scientists, new conceptualizations are offered. Also, more of the social conditions and consequences are observed and reported.

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*Before the recent increase and spread of use, however, the social class of marihuana users, in the U.S. as well as in other countries, tended to be lower.

The spread of marihuana through different segments of the society is aptly viewed as an example of adoption of an innovation (3). A given individual ordinarily goes through a number of stages before adopting an innovation -- awareness of the innovation, development of interest, evaluation or knowledge-seeking, and a trial period. Sometimes the practice is not permanently adopted, but is rejected or discontinued. Moreover, individuals differ in their tendency to adopt early or late, in comparison with others.

In one pilot study of the adoption of drug use, it was found that most young people were aware of marihuana before they were aware of heroin (3). But the average age of first awareness varied by geographic area; in some areas it was as early as the fourth or fifth grade and in others as late as the first or second year of college. The interest stage ordinarily followed from one to three years after awareness, and there was a rapid movement from interest to knowledge-seeking and trial. Evaluation was not always a rational process; some succumbed to group pressure without much thought. These findings, though superficial and tentative, illustrate the fruitfulness of social change conceptions for understanding drug use.

Another study has re-confirmed the importance that many observers attach to the drug culture, represented by multiple drug users. Comparing teenage youth who have used only marihuana with those who have used marihuana and other drugs, the authors found much more deviant and illegal activity among the latter (24). Multiple drug users, for example, were more likely than marihuana-only users to have been approached by a stranger selling drugs. They also were more likely to have introduced some to drugs. And they, more than marihuana-only users, were more likely to have been in trouble with school authorities and the police.

Hippies also typify the drug subculture and they too are more likely than non-hippie users to introduce drugs to others and to engage in selling marihuana (11). (Half or more of the hippie group in New York admitted to selling at some time; but about one-fourth of non-hippie users had also "dealt" in marihuana.)

Marihuana and crime There continues to be little evidence that marihuana use in itself causes criminal behavior. It is still an open question whether or not marihuana tends to loosen inhibitions and encourage immoral behavior, and whether or not marihuana tranquilizes users and thus deters violence.

Although not all marihuana use occurs in social settings by any means, the social features are extremely important in predicting individual experimentation, the spread of use, and the meanings of use. Economic aspects too are interwoven with the social characteristics of usage and users. Continuation of social and cultural research is therefore of prime importance.

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IV. MARIHUANA USE IN OTHER COUNTRIES

MARIHUANA USE IN OTHER COUNTRIES

The plant marihuana was known to many peoples and cultures long before it entered into the system of botanical classification in the Western World in the 18th century. The Assyrians called the plant "Quonoubou Qunnapu," and this name passed into other languages - the Hebrew "Quanneb," the Arabic "Qannob," the Persian "Quonnab," the Celtic "Quannab," and the Greek "Kannabas." It seems reasonable to believe that the similarity of names sprang from a recognition of the medicinal and/or intoxicating qualities of the plant, rather than from its use as a source of fiber.

Even today in most parts of the world where the plant is cultivated either for use as hemp or for its seed oils to be used in various preparations, it is still called by some local variant of the basic term Indian hemp. If, however, the plant is grown for human consumption for medical, religious, work adjunct or intoxicating properties, there are a variety of names which permit distinction not only by country, but in some instances on the potency of the psychoactive materials. For example, in Algeria and Morocco the hemp drug is called kif; in Syria and Lebanon, hashish el kief; in South Africa, dagga; in Central Africa, djoma; in Brazil, maconha and liamba among other names.

In India, one of the areas of most extensive use, the various preparations of the drug (in order of potency) are bhang, ganja and charas (churrus). In Jamaica the plant, not indigenous to the New World, was introduced by East Indian laborers and is still called by its Indian name "ganja." By whatever name it is known, it can be, and is, grown legally and illegally, wild and cultivated, in most countries of the world.

The use of the plant for medical and religious purposes, and as a tonic to relieve fatigue, probably predates its use as an intoxicant. Even today, for many, if not most,of the users in various parts of the world, the value of the drug lies primarily in its use in medical practice (including self medication), in religious rites,and as a work adjunct -- rather than as an intoxicant.

In many countries cannabis has been used for religious purposes. This has been particularly true of ceremonial occasions when many would partake of the drug simultaneously. This type of usage has been noted in India and among certain cult groups in Central and South Africa, Brazil, Mexico and Jamaica. This type of religious ceremony with widespread community participation and the induction of trance states in certain individuals by large drug doses is frequently connected with petitions for help concerning illness. Many primitive peoples, indeed many people in the underdeveloped sections of the world, still associate most illnesses with supernatural evil powers. Thus they find it natural to employ religious petitions to cure themselves of their ailments. In this sense, even the religious use of cannabis may be said to have a therapeutic connotation.

The Indian Hemp Commission went to great lengths to search out the meaning of cannabis to people in various parts of India and to examine its use religiously and within the different religious sects. It should be noted that it is bhang , the weakest variety , referred to in most of their comments on the religious use of the plant , not the stronger varieties of cannabis such as ganja and charas. It is true that many of the ascetics and mystics probably used enough bhang to keep themselves in a perpetual state of intoxication, a fact noted by some of the witnesses before the Indian Hemp Commission, but it is difficult, if not impossible, to find out what proportion of the whole group of ascetics these individuals constituted.

Cannabis has been used, and continues to be used, in many parts of the world as a stimulant, to prevent fatigue, in a sense as a work adjunct. This is particularly true in those occupations which are physically demanding, monotonous, dirty, non-demanding intellectually, and with little possibility of advancement. Such a description can be applied to many jobs in those parts of the world where cannabis use is endemic and widespread.

For example, I. C. and R. N. Chopra (3) note that bhang or ganja is frequently taken by laborers at the end of the day to relieve fatigue. This results in a 50 percent increase in cannabis consumption in certain parts of India during the harvest season. A common practice amongst laborers engaged in building or excavation work is to have a few pulls of a ganja pipe or to drink a glass of bhang toward evening. This produces a sense of well-being, relieves fatigue, stimulates the appetite, and induces a feeling of mild stimulation which enables the worker to better bear the strain of the daily routine of life.

C. J. Bourhill, writing in 1913 (2), states that dagga smoking was not only permitted but actually encouraged among African mine workers because after a smoke the natives worked harder and showed very little fatigue. The usual mine practice was to allow three smokes a day.

Cannabis Use Abroad - Some Caveats

Data concerning the social, psychological and cultural concomitants of cannabis use around the world have many deficiencies. In many countries what information is available is often anecdotally based or impressionistic. The number of countries in which any systematic attempt has been made to examine cannabis use by modern epidemiological methods is a very small minority. Nevertheless, there is some consistency in the international reports on the characteristics of the cannabis smoker. He is typically a young male, who, until recently at least, was from a lower socioeconomic background. These characteristics seem to be typical regardless of the potency of the material smoked - ranging from the mild variety typical in the Western world to the very strong varieties of hashish consumed in the East and Near East.

Because of the lack of cross cultural studies there is little information to indicate the typical life history of the user. We know very little about the association of use with various patterns of social interaction or even how persistent use tends to be. While many near Eastern accounts, dealing as they do with long term users, tend to give the impression that use is persistent, it is by no means clear that the users discussed are necessarily typical of what may be a far larger population of users of a greater variety of types. Certainly what we know of alcohol use in our own culture suggests that rather than some one single pattern, intoxicant use may well represent a marked diversity of patterns.

Little is known about the patterns of initiation into the use of cannabis except in a comparatively few cultures. In some, use is initiated through contact with older male users. There is probably an element of learning involved in coming to find the experience pleasurable and it is noteworthy that in many cultures pleasure per se is not an objective of use.

Apart from the therapeutic uses which are extensive and its use as a work adjunct, cannabis has often been associated with religion. Such use is, for example, extensively discussed in the Report of the Indian Hemp Commission of 1893 (6). It has been mentioned incidentally in this connection in other studies. It must, of course, be remembered that detailed study of the use of cannabis in the many cultures in which it is used, is the exception rather than the rule. Thus our data on the uses to which cannabis has been put are at best fragmentary.

In the section which follows we have attempted to summarize some of the information which is available on cannabis use and related issues in different parts of the world. It is based on information obtained from American embassies abroad as well as other sources such as reports and newspaper accounts. While every attempt has been made to use only accurate information, inevitably not all source materials have been equally complete or objective. The materials have been included in order to provide some preliminary picture of present day cannabis use on a world wide basis.

It is hoped that in future years with the compilation of better research reports a more adequate picture of the diversity of social, psychological and medical aspects of use can be provided.

English Speaking Countries

England

The Wootton Subcommittee of the British Advisory Committee on Drug Dependence received in 1967 estimates from witnesses concerning the number of people who had tried cannabis and those who used it regularly. Estimates of the number of British users ranged between 30,000 and 300,000 and the Commission itself could find no firm basis for issuing an estimate of its own. There have been, to our knowledge, no widespread surveys of student drug use such as those conducted in the United States and Canada.

In May 1971, the British Parliament enacted a new basic law dealing with dangerous and harmful drugs entitled, The Misuse of Drugs Act, 1971. The new Act replaces two previous Acts (The Dangerous Drugs Act of 1965 and 1967) which provided differing degrees of control over different types of drugs. It covers all drugs, specifies different penalties for different categories of drugs. It also affords the Home Secretary greater flexibility in the promulgation of regulations concerning different categories of drugs, as well as enabling him to shift drugs from one category to another as experience warrants.

The new Act provides for the establishment of a 23 member Advisory Council on the Misuse of Drugs to be appointed by the Home Secretary and to include at least one member with a background in each of the following categories: medicine, dentistry, veterinary medicine, pharmacy, the pharmaceutical industry, and chemistry other than pharmaceutical chemistry. This Council will help in the drafting of the subsidiary regulations and orders required to make the Act operational. It is expected that it will be several months before these regulations are published. The Council is also empowered to advise the Home Minister and the Ministers concerned with Health and Education on any matters related to drug abuse or drug dependence.

The Act categorizes controlled drugs into three classes and specifies punishments (ranging from 6 months to 14 years imprisonment) and fines (with no specific limit) for each offense under the Act. The maximum penalties for simple possession are lighter than for production, supplying, possession with intent to supply, allowing one's own premises to be used for commission of offenses (for example, the smoking of cannabis), and cultivating cannabis.

The Act appears to extend the police powers in regard to search and seizure and arrest, but the extent or the import of new powers is unclear until the implementing regulations have been published.

Canada

In Canada, the Interim Report of the Commission of Inquiry into the Non-Medical Use of Drugs (5) (the Le Dain Report) gives the results of high school and college surveys on cannabis use which were conducted in different parts of the country in 1968 and 1969. The Commission, on the basis of these published surveys as well as testimony gathered from expert witnesses, states that it is reasonable to believe (at the time of publication in 1970) that probably more than

10 percent of all high school students in Canada have used cannabis and, of course, some studies in some parts of the country have found much higher proportions. Data on use from a university level suggest that at least 25 percent of all university students have at least experimented with marihuana.

Although, at the time of this writing, the Commission has not released a second major report, it is probably a safe assumption that cannabis use has continued to rise among high school and university students just as it has in the United States. One indication of this is that the Commission itself cites a study carried out in the fall and spring terms of the same academic year which shows a rise in the percentage of users from 19.6 to 27.3 percent. Usage is defined as use at least once in the preceding six months. A second study comes to the same conclusion (1). H. David Archibald, Executive Director of the Addiction Research Council in Toronto, Ontario, reported that for several years the Council has made a detailed study of illicit drug use among over 27,000 high school students (both rural and urban) in various parts of Canada. In one case the Commission did a survey in 1968 and followed it up in 1970. The percentage of students who reported use of one or more of 10 psychoactive substances (including marihuana but excluding tobacco and alcohol) had risen in the two year interim from 20 to 26 percent, but the increase in reported marihuana use jumped from 6.7 to 18.3 percent, nearly a three fold rise.

The Addiction Research Foundation, an agency of the Government of Ontario, was set up over twenty years ago with a broad mandate to cover the entire field of drug dependence, including alcohol. It covers not only scientific research but the development of clinical services for the purposes of research, teaching and demonstration. In the early years of the Foundation's work, much of their efforts went into the field of alcoholism. In the Report to the Committee on Problems of Drug Dependence, Dr. Archibald reports that the most fascinating thing from an epidemiological point of view is that the alcohol distribution curve which had evolved during the earlier studies appears to apply also to the frequency of marihuana use. If variations in overall use and the occurrence of frequent use are examined together, there is a positive relationship - that is increases in overall use are accompanied by even greater increases in the proportion of frequent users.

The Commission is now engaged in a study in which they will attempt to assess what they call the "social toxicity" of long-term marihuana use. Two groups will live for three months in the Institute. A microeconomy will be established, based on the performance of simple construction tasks, with the earnings of subjects dependent on the amount of personal effort they expend. Subjects in one of the groups will smoke a prescribed amount of marihuana daily and will be able to use their earnings to purchase more. The researchers will attempt to determine the effects of marihuana use on such social variables as work habits, recreational activities, and aggressive behavior.

The Le Dain Commission solicited and received letters from private citizens on the non-medical use of drugs. A review of these letters, as well as expert testimony from informed observers, indicates that, as in the United States, use of cannabis has spread to groups other than the young.

Australia and New Zealand

Generally speaking, the ANZ area, that is Australia, New Zealand, Fiji, and the Pacific islands in their vicinity, is an area where the use of narcotics, marihuana and stimulants is relatively low. Use is generally frowned upon by the public and there has been careful enforcement of laws against the use of drugs with an abuse potential. Several factors account for this state of affairs: 1) the relatively isolated position of these oceanic communities; 2) the more or less rural complexion of some of these areas; 3) little, if any, use of intoxicating substances by the pre-European populations (aboriginals in Australia, Maoris in New Zealand); and 4) the lack of an illicit drug using tradition in Australia and New Zealand and little or no immigration from countries with such use.

Australia has several heavy urban concentrations, and it is from these centers that reports are emanating, indicating that there is an increasing use of various kinds of drugs, including cannabis. The same kind of finding can be reported from New Zealand. There is some production, on a very small scale, of marihuana in Australia. Most of the marihuana used in the country is reported as coming from the United States (but newspaper accounts are not clear on whether or not the marihuana originates in the United States or is simply shipped from there). Australia is not, at the present time, a transshipment point for other drugs, and Australian authorities are exerting all their efforts to see that the situation remains this way.

Most Australians are still opposed to the use of cannabis, although there is a small group of young people (who get some support from some medical practitioners) who claim that restrictions on the use of marihuana constitute restraints on their civil liberties.

The Medical Journal of Australia, August 7, 1971, reports on a longitudinal study of cannabis use in an Australian undergraduate population which is currently underway. A random sample of 168 first and second year students (72 males and 96 females) in the Faculties of Arts and Science at the University of Sydney was questioned about marihuana use, and the social and academic correlates of their drug use were established. Twenty-one subjects (12.5%) were classified as users (those who have used the drug three or more times). Nine of the subjects (5.4%) were classified as experimenters (those who had used the drug no more than twice). The modal marihuana user is male, living away from home in shared accommodations. He is unlikely to have any formal religious affiliation. Users tend to be somewhat extroverted, radical and open-minded.

Although cannabis was fairly easy to obtain during the period of the study, only six of the user group had used it more than ten times. It is evident that marihuana is not being used as a substitute for alcohol, since 60% of the combined using group stated that they also used both beer and whiskey. Thirteen percent of the marihuana users were heavy smokers (100 or more cigarettes per week) as opposed to only 2.3% of the non-marihuana users who fall into this category.

The subjects in this study, having been given guarantees of confidentiality, have agreed to be reinterviewed for several years, thus furnishing at least a start to a long-term prospective study.

Europe

France

It is difficult to obtain any idea of the actual prevalence of use of marihuana in France since statistical indicators do not distinguish marihuana from other drugs of abuse. One French specialist has estimated that the use of marihuana has doubled in the last ten years, but this estimate lacks statistical corroboration. The use of the drug seems to be centered in Paris and the major urban centers along the Riviera coast and in Marseilles.

The problem of marihuana use has been studied in France since 1838, and one of the first physicians who devoted any attention to the possible use of cannabis in the treatment of nervous and mental disorders was also a Frenchman (4).

In September 1971, a special meeting of drug specialists was called in Marseilles to examine the whole problem of drug use and drug dependence, and a new committee was set up to study all aspects of the marihuana problem in France. Dr. Naas of Columbia University was appointed Chairman and the group also includes Professor Boissier, Chief of the Neuropsychiatry Department, Salpetriere Hospital, Paris, and Professor Carteux, another French specialist.

The French public health code, most recently amended by legislation of December 1970, forbids the production, possession, trade and use of marihuana. The legislation combines prohibition of drug use with socio-medical assistance for users. The marihuana user is looked upon as a sick person rather than a criminal. However, the legislation provides heavy penalties, including loss of civil rights, heavy fines and imprisonment.

Italy

Marihuana is used very little in Italy by Italians - what there is of it is believed to be brought into the country by foreigners, particularly American, British, and Scandinavian students. There is, however, a good deal of hashish used by Italians and the traffic in this drug has increased notably during the past year. Hashish seems to be used primarily by hippies and students. However, there are practically no sociological surveys of use of either hashish or marihuana.

A bill is now before Parliament entitled "Repressive Measures Against Drug Traffic" and this bill follows the American pattern of differentiating between possession for personal use and drug trafficking. There are special provisions in this law dealing with marihuana. At the time of this writing, the bill has not yet been passed, but most observers feel that passage is likely.

Under the existing law, personal users, pushers and traffickers are all treated alike with mandatory imprisonment pending trial. Many Italians believe that youthful foreigners are at the center of the semi-organized traffic in marihuana, hashish, and a variety of other drugs. In the first six months of 1970, of a total of 168 persons arrested on drug charges, 68 were foreigners. Although there are no comparative arrest figures for the years before 1970, policemen and consular officials agree that many more foreigners are running afoul of Italy's drug laws than ever before.

There are other indications that the drug traffic is increasing in Italy. Between January and July of 1970 the police confiscated 330 pounds of hashish, more than twice the amount seized in 1969 and 30 times more than the amount seized in 1967. Police estimate that the amount confiscated constitutes only 15% to 20% of the amount of drugs in circulation.

To the extent that Italian public opinion is familiar with the provisions of the proposed law which distinguishes between simple possession and trafficking, it seems to be favorable. At the present time, sentences for marihuana use, possession or trafficking vary according to the judge. Recently, a lower court ruled that personal use of marihuana does not constitute a crime. It is believed unlikely that the higher courts will uphold this ruling. The majority of the public is strenuously opposed to the use of either marihuana or hashish.

Spain and Portugal

There are no figures available on the amount of marihuana or hashish consumed by Spanish nationals, but the Spanish government is increasingly concerned about the rising drug traffic (mainly the importation of kif from Morocco through Algeciras) which they feel is nurturing the growth of drug use in Spain. Police officials have been campaigning to make Spain's current stiff drug violation penalties even more severe. Newspapers have run sensational stories concerned with the dangers of drug abuse.

Many foreigners, particularly students, impressed with the comparative ease with which they can buy hashish in Morocco, seem to be unaware of the severe penalties if they are caught smuggling the drug into Spain - even for their own use. Under Spanish law the defendant can get off only with a fine, a brief period in jail, and expulsion if the quantity carried is less than half a pound - and if he can convince authorities that it was for his own personal use. If he is carrying a greater quantity he is charged as a trafficker and conviction on this charge means a minimum of six years in jail.

American consular officials in Spain have become increasingly concerned about the number of American students who are being picked up and jailed in Spain and have mounted a vigorous campaign to warn traveling youngsters of the dangers of trying to bring hashish into the country.

Portuguese authorities believe that drug abuse among their own people is not a significant problem at present, although they are aware that there is an increasing incidence among tourists in resort areas around Lisbon and along the southern coast (Algarve). The police believe that, at the present time, there is no large scale organized drug trafficking in the country and that the only supplies entering the country are small amounts brought in by travelers for personal use.

Denmark

The narcotics law in Denmark dates to 1955 and is in conformity with the Single Convention on Narcotic Drugs of 1961. Violation of the narcotics law is punishable by fine or imprisonment of up to two years. In June 1969, the law was amended and the penalty for trafficking was stiffened with provisions for imprisonment up to six years.

The Danish police are directing their efforts primarily against narcotics dealers. Danish users of drugs, especially hashish or marihuana, if caught by the police are usually given a warning and the drugs are confiscated. However, foreigners who are caught with even a small amount of drugs are liable to expulsion and exclusion from Denmark for a period of up to two years. In 1971, about 50 to 70 young people a month were deported from Copenhagen. In Copenhagen, 473 kilos of marihuana were seized in 1970. During the first six months of 1971, 329 kilos of hashish were seized.

There are indications that the growing drug problem in Denmark, as well as the invasion of thousands of young people during the summer who were attracted by the Dane's reputation for permissiveness, has led to a more negative attitude by the Danes toward the use of marihuana and hashish. The Danish police hope that the combined effect of expulsion of foreigners caught using narcotics and stepped up border patrols to turn away youngsters carrying narcotics will deter the influx of drug users into Denmark in the near future.

SWEDEN

The main preoccupation of Sweden continues to be the number of amphetamine users rather than the number of marihuana or hashish users. Swedish users mainline Preludin and Ritalin, both of which have now been removed altogether from the Swedish pharmacopeia. There are now between 10,000 and 12,000 addicts, about 6,000 in Stockholm and the rest principally in Goteborg and the Malmo Lund area.

The Netherlands

Probably no country in Europe has received more widespread publicity concerning its approach to marihuana use than the Netherlands. In Amsterdam weekly price quotations for various types of hashish are widely known and publicized. Municipally supported youth clubs, while not officially condoning cannabis use, are quite permissive about the use of hashish on their premises. "Dealing" in these clubs, at least in more than very small quantities for personal use, is however, actively discouraged.

Although there are penalties for personal use of soft drugs, the laws are rarely invoked. This generally known fact has been one of the factors which have played a role in the popularity of Amsterdam with young people from abroad.

An article by George Letourneau dated September, 1971 entitled, "The Cannabis Milieu in Amsterdam" which describes the recent history of cannabis use, was distributed during a recent international drug conference there. The article was made available by the Stichting Drugs Informatie, an informal drug information service widely trusted by young people. The following material is heavily based on it.

Marihuana use was introduced into Amsterdam in about 1955, primarily through jazz musicians who had foreign contacts. Later the musicians were joined by persons from Surinam who started to frequent entertainment places in an area populated by university students, artists and writers.

The author goes on to explain that cannabis use at that time implied considerable risk since many, if not most, of the Dutch people would call the police if they found that their neighbors were using illicit drugs.

Shortly after the initial interest in drug use, an article by Jan Vrijman was published in Het Parool which claimed that the sentences given to cannabis users were disproportionately severe. The basic control law, the Opium Law of 1928, did not, in the opinion of Vrijman, make the necessary distinction between cannabis and other illicit drugs.

By 1959 better quality marihuana from the Congo became available along with increased quantities of hashish. Use is described as having spread from the University to high schools. At the same time some persons in Bohemian circles had begun to experiment with ether and there was a growing use of amphetamines.

According to Letourneau, by 1960 it was possible to distinguish two main groups among the users of psychoactive drugs - cannabis users and opium users. Opium was available on the fringes of the Chinese district where usage had been tolerated in certain recognized spots for many years. By the beginning of the sixties, opium use was beginning to spread from the elderly Chinese to certain Dutch citizens, but they don't seem to correspond to any recognizable American type of drug user. Letourneau describes them as using opium "in the context of an ideology of voluntary poverty." The cannabis users have a much more familiar ring since they comprised some who used the drug for self-realization, and others who used it as a gesture of defiance against the establishment.

Members of the latter (defiant) group are probably best known through the activities of the Provos, a group of radical youngsters, who were devoted to a disclosure of the injustices perpetrated on many groups in the society by the comparatively small group at the top who ran things. The ideology accompanying hashish use by the Provos was an ideology of provocation -- they wanted to provoke action by the authorities in regard to this one act, (cannabis smoking), so they could have a public forum to expose all the other societal ills. The Provos, by and large, used what they themselves described as "playful" methods of provocation. When the Provos won a seat at the municipal elections (in the middle 60's), they declared themselves dead since they felt that they had now become institutionalized.

At least one radical section of the Provos, the Kabouters, continued to use cannabis as a form of sabotage as late as 1970. In September of that year, two out of the five Kabouters who had been elected to the Municipal Council openly smoked a "stickie" in the municipal council room. They were arrested immediately after having been evicted from the chamber but were released the same day on low bail.

At the trial it was estimated that at least 250,000 persons in the Netherlands had used cannabis during that year, and of these 30,000 in Amsterdam were regular users. The two council members were fined 50 guilders (the lowest possible punishment). In that same year, 260 or roughly half of all persons arrested on drug charges were convicted. Two percent of these people were prosecuted for trafficking. Penalties in Holland vary between a maximum of four years imprisonment and a fine of 50 guilders.

In 1968 the city of Amsterdam, prodded by representatives of various youth organizations, opened the Fantasio and Paradiso clubs, the first of a group to be given the title Cosmic Recreation Centers. The Centers were subsidized by grants both from the city and the central government.

Although the prime purpose of these clubs was to furnish recreation, the use of drugs soon took over as a major informal focus.

The illegal importation of hashish increased substantially at that time, and a substantial amount of dealing began to take place on the club premises. For this reason both places decided to close their doors early in 1969. The management of the youth centers as well as the governmental authorities who were subsidizing them frankly admitted that they had not gained enough administrative experience to cope with the increase in dealing and violence which was beginning to take place in the clubs.

However, with the closing of the two main clubs, there was unprecedented growth in the diffusion and use of psychoactive substances in all the suburban clubhouses near Amsterdam. The psychoactive substances were by no means confined solely to marihuana and hashish. Confronted with this phenomenon, the worried youth leaders went back to the government which granted them the authority to reopen the two large centers.

The clubs still continue to operate under what is tantamount to a gentleman's agreement between the government and the club managers, and the provisions have never been spelled out in the public press. The provisions do state that criminal and professional dealing are forbidden and that the use of hard drugs (which includes LSD) should be discouraged.

The Dutch authorities seem to be operating on the principle that if the use of soft drugs is tolerated, they may be able to avoid the usage of hard drugs.

There have been several untoward events, however, in the last two years, which may force them to rethink this policy. For one thing, the

Dutch authorities had no foreknowledge of the number of non-Dutch residents who would turn up to take advantage of the comparatively permissive Netherlands drug atmosphere. In the summer of 1970, historic Dam Square was inundated by youngsters who simply camped out there. There was a riot when police attempted to enforce a ban on sleeping there. This year the government set aside Vondel Park near the Leidesplen, a cafe and bar quarter, as a free al fresco sleeping quarter for their young visitors.

Germany

Drug abuse, particularly among teenagers and young people has become a major concern both among Germans and in the American community within the past year. The government has begun a two pronged approach, aimed at halting the flow of drugs into the area and educating the young people to the dangers of abuse.

According to statistics released by the State Criminal Police, the use of drugs in Bavaria has increased at least tenfold since 1967. For example, in 1967 the amount of hashish seized was 30 kilos, but by 1971 the amount had gone up to 1712 kilos. The number of persons arrested for narcotics offenses in Bavaria increased from 770 in 1969 to 2725 in 1970. Police estimate that these figures represent only 5 to 10 percent of the total narcotics traffic in Bavaria.

The figures also indicate that there is a growing use of narcotics among young people, especially juveniles. The police report that juveniles comprised 32.5 percent of those arrested for drug offenses in Bavaria in 1969 but that by 1970 the figure had jumped to 65.8 percent.

Sections of the community other than the law enforcement sector are trying to attack the problem by learning the causes of drug use and attempting to prevent young people from becoming involved. The city of Munich, which accounts for roughly one third of the drug traffic in Bavaria, has taken the lead in the approach to this problem.

In the fall of 1969, this city created a special narcotics commission, headed by Second Burgermeister Dr. Hans Steinkohl, consisting of physicians, educators, lawyers, police, and representatives of parents' organizations. In the summer of 1970, the commission undertook several measures which included: distribution of literature on drug abuse to both young people and parents; the establishment of a data bank to assess motivation for the use of drugs; the naming, within each school, of a "contact person" to whom students with drug problems can turn for help without fear of being turned in to the authorities; and the establishment of a narcotics counseling service within a Munich clinic. They also established a drug advisory home (Beratungsstelle), a specially created clinic manned around the clock by doctors and psychiatrists to assist addicts going through withdrawal, as well as to offer assistance to other drug users. This clinic has proved to be of some help but it is not adequate for the task at hand since it can accommodate only a limited number of people, and in practice it tends to admit only those suffering from the most severe withdrawal problems.

The drug problem in Bavaria is not simply a German problem, but with the large number of American soldiers, dependents and tourists scattered throughout the area the problem is a German-American one. Although there are no accurate figures on the number of troops who have used, or are currently using, drugs, the South Bavaria Branch of the U. S. Judge Advocate's office reports that approximately half the court martials in the area result from drug charges.

The United States Information Service reported in October 1971 that approximately three dozen lectures, colloquia, seminars, panel discussions and film showings have been carried out under America House auspices in West Germany and West Berlin during the past months before audiences totaling 5,000 persons. USIA also reports widespread distribution among various professional persons of specialized materials on drugs and drug abuse from the United States. Fully a third of the lectures and panel discussions were conducted by a young German pharmacologist, now at Bonn University, who has recently returned from a two year stint in the United States as an International Postdoctoral fellow in the Laboratory of Chemical Pharmacology at the National Institutes of Health. The Hamburg City Government mimeographed 400 copies of his lecture for distribution to selected officials and professionals associated with the problem of drug abuse in that city, and the Bavarian Ministry of the Interior distributed the text to all Public Health Offices in the state.

Belgium

Marihuana is illegal, but tons of it are grown legally as an adjunct to the important sugar beet crop. In the region around Tirlemont, plots are devoted to the cultivation of beet seed. Each plant is surrounded in the spring with a planting of cannabis, since it grows thickly and rapidly to a height of seven feet or more, providing a screen against the winds. Growers say this practice is standard all over Europe. In August, when the danger is over, the cannabis is destroyed under government supervision. Farm officials say that to date none of the plants has been stolen.

Greece

There is limited use of marihuana in Greece, but there are several thousand hashish users and this is a problem of long standing. It should be remembered that the Indian Hemp Commissioners, in addition to amassing testimony from all parts of India on the methods of controlling the production and distribution of the hemp plant products, also collected data on methods used in other parts of the world. One of the four countries which they included was Greece.

At the time of the issuance of the report (1893-94) Greece had no law regulating or specifically alluding to the production, manufacture or export of hashish. (At that time, Egypt believed that most of the hashish entering that country illegally came from Greece.) The sale of hashish as merchandise was allowed, but a police order of 1891 prohibited its sale and consumption in the small cafes of Athens and Pireaus. Apparently, the use of hashish had been introduced about fifteen years earlier. The police ban was based on a report of the Sanitary Board in Athens which cited the findings of the number of hemp induced psychoses in Bengal asylums as a justification for their repressive measures.

Hashish use still seems to be concentrated primarily in the area around Athens and Pireaus, and the users are mostly male. Greek authorities believe that the tightly knit Greek social structure offers protection against the widespread resort to drug use for entertainment or escape.

Greek law has always been severe in dealing with drugs and drug users, and a December 1970 law establishes even stiffer penalties.

Eastern Europe

Eastern European countries report that their major difficulty so far has been with the growing use of hashish, at least on the basis of customs seizures so far this year. Bulgaria reports a seizure of 4,000 kilos of hashish and Romanians have uncovered about 300 kilos during the same period. Both countries, but more particularly Romania, are also concerned about the increasing evidence of heroin shipments. Romanian officials are concerned that it might become a transshipment point. To date there have been no official pronouncements concerned with increasing drug use in these countries, but authorities feel that their own nations are not immune and are stepping up their border patrols to intercept drug shipments.

Russia

There are no published statistics on the use of marihuana and other drugs in the Soviet Union. Among the Turkish populations of Central Asia and in the Southern Republics of the Caucasus, the use of hashish is endemic and to a certain extent tolerated, especially in rural areas. Drug use in other areas of the USSR is probably still relatively rare. However, in recent years an increase in the number of articles on narcotics abuse in newspapers and specialized legal journals seem to indicate a growing, though still limited, problem in urban areas.

Marihuana seems to be gaining some popularity with Soviet youth, perhaps in imitation of Western youth culture, while experimentation with hashish has been noted in metropolitan intellectual circles. However, excessive consumption of alcohol still seems to be the major national problem.

There is increasing evidence that there is enough of a drug problem in several areas of the country to justify the tightening of controls. Georgia is one such example. This strengthening of the laws was praised by many legal experts in Moscow.

Narcotics convictions, including those for pushers, carry prison terms from one to ten years, with three years the apparent median for first offenders. Recidivists and large scale traffickers can receive sentences up to 15 years. Paradoxically, however, simple possession is not a criminal offense in the two largest constituent republics, the Russian Federation and the Ukraine. There is increasing discussion of the need for a nationally directed drug abuse program within a uniform narcotics code.

Near and Middle East

Cannabis use has been widespread in Near Eastern countries for a much longer period of time than in Western countries, so the literature is much more extensive from those regions. However, several cautions should be borne in mind when considering these studies: 1) Most, if not all of the studies report on the use of hashish, a much stronger form of cannabis than that currently in use in the United States; 2) The use of biased samples (study groups frequently drawn from prison populations or exclusively from members of the lowest economic groups); 3) The lack of adequate control groups; 4) Frequent failure to consider the implications of the fact that cannabis tends to be mixed with other drugs (tobacco, dhatura or more rarely opium) or the corollary question of the extent to which users of cannabis are also users of other drugs.

Undoubtedly one of the most critical features differentiating accounts of the effects of hashish on users in underdeveloped countries and the use of cannabis in the United States has to do with the level of nutrition. Obviously the use of any drug will have a far greater effect on people who are chronically underfed. As far back as 1894, an English writer, surveying studies done in the previous two decades in Indian mental hospitals, said that the violent intoxicating effects of ganja or charas are less marked or not seen at all in persons having a regular and wholesome supply of food.

The question of the duration of the use of cannabis, as well as the strength of the form of cannabis employed, are extremely important issues from the standpoint of public health. Observations of Eastern writers tend to be at odds with those from other parts of the world. To begin with, it is usually safe to assume that in talking about persistent use they are speaking of persistent hashish use, but this is not always clear and yet this is a crucial issue. Most Eastern writers imply that once the cannabis (hashish) habit is established it is likely to last as a daily habit for many years. However, actual longitudinal data on representative samples of persons initiated to its use are seldom if ever cited. In other parts of the world there are indications that some discontinue use after adolescence or use it only intermittently.

Israel

Israel reports an increasing amount of hashish use among university, and even some secondary school students. In his study of the sociological and epidemiological features of hashish use in Israel, Miller points out that several features peculiar to the State of Israel must be borne in mind in considering the use of hashish there (7). Geographically, Israel is in the midst of neighbors who for long have had a drug culture, preeminently the use of hashish, but with a strong opium subculture. The country has, in the past, served as a transshipment point for the transport of drugs and its border areas still serve the same function. Before the formation of the State of Israel, there seems to have been a very small nucleus of hard-core addicts made up primarily of marginal people from Eastern Jewish cultures and a few Westerners who were probably medically addicted. The numbers of both of these groups increased after statehood with the beginning of mass immigration.

The Jewish immigration from the Middle East brought a mass of people from the hashish cultures, and the number of these Middle Eastern and North African migrants relative to that of European Jews increased. Some of these immigrants had belonged to criminal groups in their home countries, and many of them were addicted to hashish as well as to the use of opium. Most of the migrants had problems achieving social or economic status in the earliest years of their stay in Israel, primarily because of the great difficulties in acculturation. Some of the children of these migrants, unable to adjust to the highly competitive Israeli society dominated by European born Jews, became school dropouts and delinquents and are over-represented in the addiction figures.

Some Israeli Arabs and Oriental-born Jews use hashish socially, but up until the present time heavy cannabis use seems to have been associated with the criminal elements of society. There is some evidence of its initial extension to non-delinquent but marginal youth of Middle Eastern descent.

After the Six Day War in 1967, use of hashish increased because of the greater availability of the drug and the comparative ease of obtaining it. In addition, since 1967 there have been an increasing number of youngsters from Western countries who have come to study or visit in Israel, and many of them have brought with them their cannabis smoking habits. According to police reports, there were twice as many Israeli drug offenders in 1969 as in 1966 before the Six Day War. The same reports point up the increasing drug traffic. In 1966, 111 kilos of hashish were confiscated, and in 1969, 3,179 kilos. The amount of opium confiscated was 40 times greater than that seized before the War. The Old City of Jerusalem seems to have become a center of the drug trade, and arrests there indicate that many foreigners are engaged in the business of smuggling hashish to Europe and America.

Israeli social scientists stress the fact that there are no adequate figures available on either incidence or prevalence of use of cannabis among students or other groups in the population. However, there is some evidence that use is increasing among adolescents and for some of them it may represent a disaffection with the life styles of their elders.

While drug abuse is a more serious problem in Israel than it was before the 1967 Six Day War, it has not become an acute problem to the degree it has in other nations largely because the population generally is alert and well educated and official counter measures have been vigorously pressed. Israel is apparently not a transit state for opium or its derivatives nor are they a significant problem there. Because of publicity given to convictions in 1970 and 1971, cases of hashish are on the decline.

Lebanon

Lebanon is one of the prime hashish producing areas of the Near East and most of the country's production is concentrated in the Hermel area. An article which appeared in l'Orient Le Jour on June 20, 1971, (a leading Lebanese newspaper) gives a scholarly and poignant picture of the life of the cannabis growers, a picture which could probably serve as a prototype of the lives of other growers of marihuana and of opium poppies in other undeveloped areas of the world. The article also gives some insight into the reasons why hashish production has become so deeply ingrained in the area and why its eradication is so difficult.

The Hermel area is exceedingly poor -- there are practically no individual homes and many families live together in extremely primitive dwellings. There is no public water distribution, so the people must either use the public fountains or dig their own wells. Roads are almost nonexistent, and the connecting links between villages are usually mule tracks. There are few schools and no hospitals. In the entire district there are only a few doctors. In the village of Hermel (population of 6,000) there is not even a pharmacy. There is practically no electricity.

Most of the arable land is owned and cultivated by tribal members (a tribe consists of a number of families all of whom have the same name). Some of the land is cultivated by tenant farmers (métayers who do not belong to tribal groups and are at the bottom of the economic and social ladder. The living conditions of the owners and the tenant farmers are usually equally miserable.

Planting hashish is for the peasant of Hermel the equivalent of planting tobacco or wheat. None of the hashish is consumed locally. For the farmer, it is simply a crop which will permit him to augment the family budget. The hemp crop has several advantages for the farmer - it can be planted in place of wheat in the framework of a three crop rotation of crops even when the land is left fallow. In addition, the hemp plant does not require irrigation. The picked and dried hemp produces its own seeds which will be used during the course of the following season. The drug itself is sold by the hundred weight (quintal). In the past this was worth LL 1,000, as compared to wheat (LL 25) and tomatoes (LL 40). Even when the central government has attempted at various times to crack down on the production of hashish and substitute various food crops, this has proven to be impractical since there are no roads to get such bulky produce to market. The hashish is resold to traffickers who are recruited from the larger towns and especially from a group called the "abadhays" ("tough guys" of the tribes) who have direct links to the tribal chiefs.

At times the central government, in an attempt to consolidate power and reduce the power of the tribal chiefs, has permitted the farmers of Hermel to grow and sell Indian hemp. At other times they have attempted to introduce the production of substitute crops such as sunflowers. However, the cost of production of the sunflowers was higher than that of hemp and, of course, the crop brought in much less.

To date, there has been no successful attempt to introduce a viable substitute crop for hemp and the farmers of Hermel, even with the hemp crop, live at a bare subsistence level.

IRAN

The use of cannabis in Iran up until the present time has been negligible and the penalties for use and smuggling have been light compared to those for smuggling opium and heroin. Today the use of hashish is becoming more prevalent, especially among students. Recent statements by government leaders indicate that if smuggling and the use of hashish is increased the state might have to re-examine its laws with a view to increasing penalties.

EGYPT

In Egypt, expert observers estimate that the current number of opium addicts is about 150,000 which would include about two percent of the adult male population. Hashish is widely used by adult males and is readily available.

The use of hashish has long been a problem in Egypt and in other Arab states, and there is a well-established trafficking pattern to Egypt from Lebanon. Opium is imported primarily from Turkey with some lesser quantities coming from Iran.

Usage in Latin America

Although the New World has a much greater array of narcotic and hallucinogenic plants than the Old World (plants utilized for religious, medical and recreational purposes) cannabis is not indigenous here. Schultes, the famed ethnobotanist of Harvard University, states that out of the hundreds of thousands of plant species, perhaps about sixty have been utilized as hallucinogens, and of these sixty only twenty have been used to any great extent and most of these are found in the New World. (8)

There is no mention of cannabis in all the accounts of North American Indian medicine assembled by early travelers to this continent. Similarly, in the extensive collection of materials on Aztec Materia Medica assembled by Sahagun shortly after the Conquest, one finds no mention of this herb. Art historians and archaelogists who are specialists in South American artifacts point to the absence of any representations of the plant in cult objects, whereas there is an abundance of such representations for the "magic mushrooms",to cite but one example.

The plants may have been introduced by the Spaniards to Mexico, Central and South America, either at the time of the Conquest or shortly thereafter. It should be remembered that Spain had long been occupied by the Moors and commerce with them continued long after they had been expelled from the country. Cannabis was and is used in Arabic medicine, and its use both as a medicine and as a refreshing tonic may well have been known to the common people. The history of the introduction of the plant to Latin America remains to be written, and it is a curious irony that with the current veritable explosion of research work dealing with cannabis comparatively little attention so far has been paid by historians or anthropologists to the phenomenon of its spread.

There is a difference of opinion among experts about Brazil, with some persons claiming that cannabis was introduced by early Portuguese explorers, and others who state that it came in later with the advent of Negro slaves. The words for cannabis in Brazil (which include machoma, ciemba, liamba, diamba, and maconha) are closely linked to some words for the plant from various sections of Africa. For example, in West Africa the names include yamba, diamba, and in South Africa, in addition to dagga, one also finds djamba, liamba and riamba.

Negro slaves in Brazil and in other parts of the New World were recruited from various sections of Africa and it is not possible to assume that all of them were knowledgeable about cannabis and its use (whether medicinal, religious, or recreational). Moreover, the conditions of the slave ships themselves would certainly have militated against the carrying even of seeds of the plant. Some authors have pointed out that in the state of Bahia (still one of the areas of highest use of cannabis in Brazil) there was a comparatively high proportion of Mohammedan Negroes who may well have been acquainted with both the medical and recreational uses of cannabis.

It seems unlikely, however, that cannabis played any major role in the medical armamentarium of early Brazil, one that depended heavily on the herbal knowledge of the slaves in the major plantations. It is not, for example, one of the plants mentioned by Freyre in his monumental studies of Brazil (including Masters and Slaves), although he goes into great detail about many other food and medicinal plants introduced into Brazilian diets and home medical remedy supply cabinets by the slaves.

Studies in Cuba (Lydia Cabrera) do not mention the plant among those whose therapeutic efficacy was known and prized by Negroes in that country in the early and middle decades of this century. No mention of cannabis appears in studies of Haitian herbs, for example.

We know that cannabis was not introduced into Jamaica and Trinidad and some other islands of the West Indies until after Emancipation, and in fact is still called by its East Indian name of ganja. It is interesting that in the United States, whose population once included Negro slaves, the possibility has rarely been raised that they were the ones who were the first to recognize some of the euphoriant qualities of the plant. Hemp was widely cultivated in the United States but the medicinal values of the plant became known only in the latter half of the nineteenth century and then by way of introduction from England. It is widely assumed that use of the drug, either as a refreshing tonic or as a mild euphoriant, did not take place in the United States until the 1920's, and Mexican laborers introduced it.

Although there is some use of the drug in religious ceremonies in Northeastern Brazil, by and large the religious cults of Negroes in Brazil and in the Caribbean islands which stress trance or possession and show the strongest evidence of African inspiration do not use drugs of any kind to induce possession. (9) This is true of candomblé groups in Brazil, of Vodun in Haiti, of Shango in pre-Castro Cuba (and post-Castro groups in Miami) as well as of Shango groups in Trinidad. Bastide points out that some Negroes in the Northeastern parts of Brazil (the sertao) where they constituted a comparatively small number vis-a-vis the native Indian groups, joined the Indians and created religious groups known as catimbo. The Indians were accustomed to using hallucinogenic snuffs in their ceremonies, and according to Bastide the Negroes substituted cannabis for the use of these snuffs.

There are no completely adequate usage figures available for any of the Latin American countries, although there is mounting evidence that many of them are becoming increasingly concerned with the spread not only of marihuana use, but of other drugs as well, to sons and daughters of the middle and upper classes. Many countries maintain that this spread is directly attributable either to the influence of the United States or European countries, and tend to discount the possibility that the adolescents may have learned the use from lower class members in their own societies.

Mexico

Mexico for many years has been aware of the use of marihuana in the slum districts of many cities, despite the fact that there are severe sentences either for possession or trafficking in the drug. The government of Mexico has always cooperated with the United States (primarily through its enforcement agencies) to cut down on the cultivation of both marihuana and opium poppies, as well as to intercept shipments to the United States. (Most marihuana in the United States probably comes from Mexico.)

The Mexican law is severe for either possession or trafficking in marihuana. In addition, the new Agrarian Reform Law provides for the confiscation of privately owned land used for growing marihuana or opium poppies. Mexico was a signer of the Single Convention on Narcotic Drugs in 1961, but until 1964, when the fortieth signatory was obtained and the Convention was made operational, there was comparatively little attention paid either to the farmer who was apt to have small plots under cultivation or to the lower class users in the slum areas of the big cities. Even today with an intensive, well-publicized campaign to eradicate marihuana plots, many observers feel that most of the zeal is centered in the Mexican Army and in the Federal police forces.

The states in which marihuana is grown include Sinaloa, Durango, Chihuahua, Michoacan, and Guerrero. Some of these states are among the poorest in Mexico, and at least two of them have been among the heaviest suppliers of Mexican labor to North American farms.

A Washington Post dispatch, August 18, 1971, points out that "many of the poppy and cannabis farmers, who are tired of growing corn that does not bring much profit, defend their property fiercely and shoot-outs with the soldiers are very common. Now farmers are also threatened by loss of agricultural rights or losing their land altogether if they are found growing forbidden plants."

It is only in the last few years that use of the drug has spread from the lower classes to the sons and daughters of the upper classes, and that Mexican officials have admitted that Mexico has a drug problem of its own. A study made public in late July 1971 by the Mexico City Medical Center reported that of 7,500 students polled in grades 7-12, 15% reported the use of some type of drug or hallucinogen. Of those who admitted the use of some type of drug, 80% smoked marihuana. Usage had doubled compared to the previous year.

To our knowledge, there have been no studies made of university students in Mexican universities. The Washington Post, August 18, 1971, says that "university students associate marihuana with the affluent minority and also with the young thugs who often terrorize left-wing students. The left sees the growing use of marihuana as another sign of United States cultural imperialism." It should be remembered that the university students mentioned here are enrolled in the National University of Mexico, a state supported institution. There are comparatively few private universities in Mexico, in the North American sense of the term. In addition, many of the sons and daughters of the wealthier classes attend colleges and universities in the United States or other countries.

Following the publication of the Mexico City Medical Center report on student drug use in July, there was a good deal of coverage in Mexican newspapers, including items such as these: 1) Dr. Carlos Tornero Diaz, Director of the Children's Hospital in Mexico City, a hospital primarily for the mentally ill, reports that about 12% of his patients enter as a result of some "drug connected disability." Unfortunately, we have been unable, at the time of this writing, to secure any more specific information as to the type or duration of these drug connected disabilities; 2) one columnist for Excelsior's Ultimas Noticias (one of the most widely read newspapers in the capitol city) reported that between one and a half and two tons of marihuana are smoked weekly in Mexico City.

Mexican law is extremely severe in dealing with buyers of drugs - and punishment is much more severe than in the United States. Sentences start with a minimum of two years, but lately they have been running as high as seven years, with little distinction made between possession of marihuana and heroin. United States Embassy officials estimate that at least a thousand Americans are deported every year on drug charges.

The rest (and there are over 250 of these) are now being held in Mexican jails. Because of the severity of the sentences, as well as the difficulties of life in Mexican jails, U. S. Embassy officials are kept extremely busy with anti-drug campaigns aimed at American students who come either for short stays as tourists or enrollment in colleges and universities which cater primarily to North Americans.

Venezuela

In Venezuela, narcotics statistics date only from 1968. The quantity of marihuana confiscated declined slightly from 1968 to 1969 but approximately tripled in 1970. However, the maximum total seizure in any one year has never exceeded 254 pounds. Venezuela, because of its geographic position, lends itself as a transshipment point for narcotics to and from all of South and Central America, as well as points north to the United States and Canada. In addition, Venezuela's proximity to the Andes mountain people, long known as producers of marihuana, coca and cocaine and the length of the Colombia-Venezuela border (with Colombia a major producer of cannabis), make Venezuela susceptible of transition into both a buyer's and seller's market.

In October of 1970, the Venezuelan Chamber of Deputies created a special commission charged with investigating the consumption and traffic of drugs in Venezuela. The report of this Commission should be available later this year. In addition, on September 1, 1971, the Venezuelan Cabinet issued Decree No. 684 creating a Narcotics Commission to study plans and programs for combatting the traffic in drugs, as well as treatment plans for the rehabilitation of addicts.

Colombia

Marihuana grows in many parts of Colombia; and although it is illegal to possess, sell, purchase or use it, it is readily available through clandestine sources. Further, the application of the law to use in certain circumstances, such as the privacy of one's home, has not received judicial interpretation, and, to our knowledge, no arrests have been made for this. University authorities in all of the major Colombian cities agree that within the past four years use has increased markedly among students, but to the best of our knowledge, no actual surveys on student use have so far been published. University administrators in Bogota estimate that at least 25% of their students are regular users of cannabis.

Some North American medically trained observers report themselves mystified concerning the number of reports of acute toxic reactions resulting from just one use of the drug. If such reports are accurate, part of the explanation may lie in a difference in drug potency. One young American in Bogota reported that he had smoked marihuana sporadically in the United States for several years before coming to Colombia, and since his arrival in the city he had tried marihuana twice. Both times his reactions had been so violent that he became frightened and vowed not to touch the drug again until he left the country.

In Bogota there has been no systematic study of any kind done with chronic marihuana users, and in fact information on the existence of a presumably fairly sizeable population is limited to statements concerning their marginal position. Up until about four years ago, people smoking marihuana were called "marijuaneros" which is roughly synonomous with "bum." Certainly it means someone at the lowest level of society. As late as the 1940's, one of the main thoroughfares of downtown Bogota, today a fairly respectable street, was known as the street of the marijuaneros, and it was common to see people intoxicated from the drug there.

In Cali, some observers believe that marihuana use has not only penetrated to the University, but that it is beginning to permeate all social classes. At least one behavioral science researcher, presently at the University of Florida, had identified a population of long-term users in Candelaria, a slum area of Cali, several years ago. Unfortunately, this study had not been centered on marihuana users as such - the information had just been amassed in the course of collection of other kinds of data.

There are undoubtedly many other studies of just this sort, or researchers could go back to search their own field notes for observations about marihuana use in a population or an area they were studying for some other reason. For example, one Colombia researcher has worked for some twenty years on studies of Negro culture in the country. A good part of his basic research was carried on in the Magdalena Valley, in northeastern Colombia near the border of Venezuela. When questioned, he recalled that he had often seen men smoking (marihuana) during their rest periods and at the close of the working day. Magdalena is widely known as one of the major marihuana growing areas and it is probable that use is fairly widespread there and has been for many years.

Dr. Reichel-Dolmatoff, one of the best known Colombian social anthropologists, did archaeological research in the Magdalena Valley in the 1940's. He recalls that his laborers regularly smoked marihuana in their rest periods. At that time marihuana had already been made illegal and to escape police reprisals and confiscations laborers grew the plant in a small pocket of soil deposited in the tops of palm trees. Some commercial marihuana was grown in small plantations in that area at the time of his studies, but the development of large scale growing operations seems to be more recent. Other observers have pointed to sites on the Magdalena River where long-term marihuana use is very widespread.

In Cali, one psychiatrist reports that about 50% of the patients who enter the mental hospital have some record of marihuana use. He does not believe that marihuana has been the leading factor leading to their psychotic state. He believes that marihuana, if anything, has simply served to trigger the dormant psychoses. It should be emphasized that this is not a controlled study - it is simply the report of the impressions of one psychiatrist.

Some blue collar informants in Cali have recently notified University of Florida researchers that, contrary to the opinion of many professional psychiatrists and medical doctors who tended to think of all chronic marihuana users as being marginal members of the society economically and in other ways as well, there were established populations of users who were managing to function both economically and socially. These populations included mechanics, manual laborers, as well as people who do odd jobs.

Use of marihuana seems to be much more widespread on the north coast of Colombia than it is in Bogota. In Barranquilla, marihuana, according to well-informed respondents, is sold openly even in public places. Use is common among day laborers, office workers, university and high school students. It has even begun to penetrate the grade schools.

The major source of supply seems to be the Magdalena River Valley and the Sierra Nevada de Santa Marta. Though marihuana is now grown in practically every climate and altitude in Colombia, and although there are small plantations even on the Bogota plain, people all over the country agree that the highest quality marihuana is that from the Sierra Nevada de Santa Marta. This variety is called Santa Marta Dorado. The second best product comes from the Magdalena Valley.

One anthropologist who has worked for many years on the North Coast reports that he can only guess at the history of marihuana use in Colombia, but the introduction must have been many years ago. He states that when he began his professional career twenty-three years ago, use of marihuana was widespread among the working classes. This use through smoking, he believes, has not increased among the working class but is growing among the middle and upper classes.

In Cartagena, many university officials believe that marihuana use is concentrated in the slums and that almost all slum dwellers are chronic users. However, one man who has worked for years in one of the largest slums in Cartagena believes that no more than one percent of the slum dwellers are chronic users. He believes that use is growing, however. One of the other workers in the same slum area reports that there now seems to be a tendency for people to organize clubs of marihuana users who get together to smoke, much as persons would drink alcohol in a bar. These club organizers believe that marihuana is much less damaging than alcohol. Some other informants have told these social workers that some persons turned to marihuana to get rid of their addiction to alcohol.

Argentina

In Argentina, most observers feel that the main drug of abuse is marihuana, although there is increasing evidence that other stronger drugs are being smuggled across the border from Paraguay. The Argentine government is very concerned with growing drug use, and the press reports that in September the Social Welfare Minister met with government officials and private individuals to draw up a "large scale offensive" aimed at drug peddlers catering to the 12-22 year old buyer.

In October, the Argentine press reported that the President sent to the Chamber of Deputies a new draft control law for the control of narcotics. Narcotics is defined as all natural or synthetic substances "capable of creating states of dependency harmful to health." The bill would establish a national registry for narcotic substances, and require that all persons who deal in narcotics for commercial or industrial purposes register within 30 days of the establishment of such a register. The Ministry of Public Health is given the responsibility of preparing a list of narcotic substances as well as the establishment and control of the registry.

The bill would further provide that all drugs be sold only pursuant to a prescription prepared by a physician registered with the Ministry of Public Health, that the pharmacist keep detailed records of sales, and that auditors from the Ministry of Public Health be required to inspect these records. Penalties are imposed for failure to comply with these provisions.

The penalties concerned with unlawful or clandestine importation or exportation of narcotics have been strengthened and now provide for 10-30 years imprisonment and a fine four times as great as the value of the narcotics seized. One unique feature (at least of the draft proposal) is the proviso that any government official involved in any way in the drug traffic be given the maximum penalty corresponding to his degree of participation.

Paraguay

In July of 1971, Paraguay and Brazil signed a major agreement concerned with cooperation on public health matters in the border areas. The agreement is basically one concerned with the exchange of public health information between the public health authorities of the Brazilian states of Matto Gross and Parana, and the contiguous Paraguayan departments. The agreement sets up a bilateral working group to accomplish this purpose. Priority attention is to be given to the eradication of malaria, smallpox, yellow fever, leprosy, tuberculosis, and venereal disease.

Primarily, through the initiative of the government of Paraguay, special emphasis was placed on drug abuse control. Studies are to be made of the extent and form of use of narcotic and hallucinogenic drugs not only in border areas but nationwide. Medical and pharmacological controls are under consideration as well as cooperative educational programs. A similar agreement with Argentina is a further possibility.

There are at present no laws concerned with narcotics offenses embodied in the Paraguayan criminal code. One of the most prominent Paraguayan criminal lawyers has now prepared a draft of proposed legislation which will remedy this situation, and the draft is expected to be considered at the next session of the Paraguayan Congress. The draft also contains provisions for a drug abuse prevention and education campaign.

Brazil

The problem of drug abuse did not exist on any significant scale, or at least did not seem to cause any significant public concern in Brazil until about 1921 when the first laws appeared on the books The present Brazilian penal code, issued in 1941, incorporated all previous legal provisions in its Article 281 and states that it would be considered a crime to "plant, export, import, sell or carry narcotic substances," and that those found guilty would be punished with from one to five years imprisonment. The understanding of the Supreme Court at the time, however, was that those who were caught in possession of drugs for personal use would be treated as sick people rather than criminals.

Within the last three years, however, since there has been a growing use of illegal drugs, particularly marihuana in Brazil, the Federal government decided to change the provisions of the penal code and in December 1968 it issued a decree - Law No. 385.

The new version of Article 281 provides that people who illegally possess drugs for personal use are also punishable under the law. This law also increased the penalty for those involved in trafficking.

The Government of Brazil is apparently acting on the premise that the drug problem represents a threat to national security and has recently initiated a major campaign to warn the public of the drug menace. To date in this campaign there has been little attempt to separate the various drugs of abuse either on the basis of the present prevalence of use (to say nothing of incidence) or on the varying abuse potentials of differing drug classes. Most informed observers believe that the drug most used in Brazil is marihuana, followed by the stimulants and tranquilizers. They believe that the traffic in cocaine and heroin is relatively minor.

Even among those involved in suppressing the illicit sale of narcotics there is little hard information on the origin, distribution network or consumption patterns of the Brazilian traffic. It is assumed that the user problem centers in the Sao- Paolo- Rio- Belo Horizonte triangle. However, there is a long established production and heavy consumption pattern in the Northeast, centering around Salvador, which is reputed to be one of the principal transshipment centers of marihuana from that region, as well as of cocaine from Bolivia. Reliable information on the price levels of various narcotics is also lacking. The price scale for marihuana in the Rio area might vary as much as from 800 U. S. dollars per kilo for marihuana coming from Paraguay, to only a few dollars per kilo for marihuana coming from the Northeast of Brazil itself. Some marihuana reportedly enters the country from Venezuela and Bolivia as well.

Up until a few years ago, cannabis was sold openly in marketplaces under various names which include maconha, diamba, herba de sonho (dream herb). Today the government campaign against drugs is focused to a large extent on the commerce and use of marihuana. There are daily reports of arrests for selling, transportation, and use of cannabis. It is not clear what the specific powers are of the various levels of police - federal, municipal, state and military.

The President of Brazil sent a message to the Congress on June 25, 1971, which was concerned with the whole area of drug abuse, and is considered of sufficient importance to be included among the President's limited list of "impact projects" which will receive priority treatment.

The proposed law contains, inter alia, the following provisions:

1. Loss of government financial aid to institutions which fail to cooperate in drug control.
2. Educational programs to be conducted in all schools, designed to prevent drug abuse.
3. Dismissal of school principals who fail to report drug traffic within their schools.
4. Cancellation, for the rest of the scholastic year, of the registration of students found carrying drugs at school.

Some of the most controversial aspects of the law have to do with the proposals for treatment of addicts, and those dealing with summary trials of persons caught in the act of carrying, selling, or buying drugs. Compulsory treatment in a hospital is asked for addicts who are acquitted on grounds that, because of drug dependence, they were unable to understand the illegal nature of their act. Psychiatric treatment will be mandatory for addicts between 18 and 21 years of age. Addicts under 18 may be compelled to undergo treatment until they are fully rehabilitated. In all such cases, incarceration will end as soon as an addict shows sufficient evidence of rehabilitation. The summary trial provision provides that a defendant will have to be indicted within 48 hours, and the judge will have a maximum period of 20 days in which to pass sentence.

The present Penal Code which has been in effect since 1941 also provides for the compulsory treatment of drug addicts as well as criminals suffering from mental illness. These provisions have rarely been carried out because of the lack of specialized treatment facilities. Moreover, the proposed law requires a judge to order psychiatric treatment for addicts over 21 years of age only when they are acquitted on the grounds that, because of drug dependence, they were unable to understand the illegal nature of their act. Since the type of drug most commonly used in Brazil is marihuana, and of a type not normally sufficiently potent to produce this kind of effect, the net result will probably be that the majority of addicts in Brazil will continue to receive prison sentences and fines rather than psychiatric treatment.

The proposed provision for summary trial within 20 days is viewed as unrealistic by most observers. Both law enforcement and judicial authorities are unanimous in saying that it is impossible for the police to present a laboratory analysis of confiscated narcotics within the period of time set forth in the proposed law, and the

Brazilian courts simply cannot operate at the speed expected of them. Trials of persons arrested on drug charges take at least three months and in some instances much longer.

Cannabis was probably imported from Africa to Northeastern Brazil early in the colonial period and has been in use for well over two centuries. The area of its supposed introduction (Bahia State) and a state north of Bahia, Alagoas, are still among the areas with the highest concentration of users. In 1941 a team of anthropologists (9) studied a group of Tenetehara Indians in Maranhao State. At the time of the study and today as well, the Indians were regular users of cannabis which they themselves cultivated. The use of cannabis by these Indians goes back at least to the early part of the 19th century, according to brief reports from travelers. Wagley and Galvao, although they translated the local term diamba into English as hashish, had this to say about marihuana use among the Tenetehara (9, pages 41-42):

> The African Negroes, who were brought to Brazil by the first European colonizers as plantation laborers, were undoubtedly responsible for introducing hashish into this region. It is in wide use by both the Tenetehara and the Brazilians of this region. Cultivation follows closely the same procedures as those described for tobacco. Hashish is sown in baskets in fertilized earth and then transplanted to gardens near the village. The flower and the leaf are dried in the sun to be smoked in cigarettes similar to those made of tobacco. Since hashish is said to be "strong", four or five men smoke the same cigarette. Brazilians smoke the leaves in cigarettes or in water pipes made of gourds. Although the Indians speak of cases of hallucinations caused by hashish, the Tenetehara generally use hashish moderately. In shamanistic activities its use to induce trance is

> frowned upon. There were ugly rumors in Januaria village that the young *paze* called Vaqueiro has to smoke hashish to get his spectacular trances. Tobacco is the only traditional stimulant for shamans.

Brazilian public opinion on marihuana use and users seems to be as widely divided as public opinion in the United States. Some Brazilians believe that no distinction should be made between marihuana and the addicting drugs, and that both addicts and traffickers should be given equal treatment under the law. Others would have the law make a distinction between marihuana and hard drugs, no punishment be given to users, since the drug is a social drug, no different from alcohol. Some persons openly recommend legalization of the drug, although they are in a comparatively small minority at the present time.

Central America and the Caribbean

The origin of marihuana use in Costa Rica is unknown, but it has been in use for many years, not only by members of the working class but by members of the middle and upper class as well. In contrast to other Latin American countries where reports of widespread use by adolescents from the middle and upper classes date from only the last four or five years, Costa Rican informants drawn from the professional class state that cannabis use was extensive in the early 1950's. In one working class suburb of a major Costa Rican city, working class informants have told some researchers that years ago, when traffic in the drug was more free than it is today, marihuana was sold openly on many street corners in their neighborhood as well in the central city market.

At that time, the customary method of selling marihuana was by the pound. Today it is sold much more frequently in the form of single cigarettes or small bags containing enough material to make three or four cigarettes. Even today individuals from the middle and upper classes come to the working class suburb to make their purchases.

The drug is apparently used in three ways. The most common type of use is by smoking. Marihuana cigarettes sell in the capitol city for approximately sixteen cents apiece. Marihuana tea is used in the treatment of pain in general, but for stomach illnesses in particular. This use seems to be very widespread and many nonsmokers use cannabis in this form. There is some smoking of marihuana in pipes by members of the more liberal student groups.

Indentured laborers from East India, imported to Jamaica, Trinidad and other British Caribbean possessions to replace Negro slaves after Emancipation in the mid-nineteenth century, brought the cannabis plant and cannabis usage with them. Cannabis is still called "ganja" in Jamaica and Trinidad although the less specific term "herbs" is coming into more ordinary use in Jamaica today. The East Indians not only brought ganja with them, but also the multiplicity of uses which the drug may serve. These included its use as a work adjunct, as a medical aid for the treatment of various physical and psychological illnesses, as part of religious cult ceremonies, and as a recreational drug. Most observers agree that the lower-class Negro inhabitants of

Jamaica adopted the drug almost immediately (the first Jamaican laws against the cultivation and use of cannabis were passed in 1914), but the usage in Trinidad (except among the descendants of the original East Indians) did not catch on to any great extent until the last five or ten years.

It is estimated that about 40 to 50% of the male population of Jamaica are daily cannabis smokers. Initiation to the use of the drug is in the early teens or even earlier. Until about five years ago, smoking was confined primarily to members of lower class working groups, in both urban and rural settings. Now usage has begun to spread to young members of the middle and upper classes.

The workers use cannabis as a work adjunct; they say it makes them "feel work". They employ ganja much as persons in the United States use the early morning cup of coffee and a cigarette, and daily coffee breaks to help them through the day's chores. The fishermen claim that it helps to keep them warmer, and the canecutters say that it wards off fatigue.

Non-smokers employ cannabis in the preparation of bush tea which is used in the treatment of a variety of ailments, such as upper respiratory and abdominal illnesses and dysmenorrhea. Ganja is also mixed with rum to produce liquid preparations used for various sicknesses. In some parts of the island babies are bathed in a ganja infusion soon after birth. This is interesting in view of the reported antibacterial action of topically applied cannabis. Observers report that cannabis is used as an all purpose drug similarly to the way we use aspirin.

Although there is still some religious usage of ganja by East Indians in Jamaica and Trinidad, it does not seem to play such a major part in their ceremonies as it does, for example, in Surinam. The Rastafarians in Jamaica probably put more stress on the religious aspects of ganja use than any other group on the island. They are a chiliastic cult which sees Emperor Haile Selassie of Ethiopia as God and stress a return to their African homeland as a primary goal. The Rastafarians call themselves "the chemists of the divine herb" and use cannabis in all forms - for smoking, for medicinal purposes and in cooking. This group recognized long before research verified it that both the male and female plants contain psychoactive material.

There is no known usage of cannabis in Haiti, either as a recreational drug or for medical or religious purposes. The famous Vodun trance state does not depend on any kind of drug for induction.

Although there are reports of widespread cannabis use in Honduras, Guyana, Surinam, French Guyana and Panama, there are, to our knowledge, no published data available on prevalence.

Africa

Ghana

In Ghana in July of 1971, the Minister of Health, in a nationwide radio and television broadcast, launched a government campaign against the use of two drugs, both of which he labeled as dangerous. One of the drugs was amphetamines, the other cannabis (called "wee" in this country). Amphetamines seem to be used primarily by students and cannabis by members of the semi-skilled and laboring groups. The Minister noted that illegal cultivation of cannabis was on the increase and pointed out that in 1959 about 93 kilos of marihuana had been discovered and destroyed, but that by 1969 the figure had increased to 193 kilos. The Minister stressed the need to educate Ghanians, particularly the young, on the adverse effects of drug use.

Nigeria-Togo

The warning from Ghana has been echoed recently by officials of Nigeria and Togo who have commented on the growing use of amphetamines and cannabis by young people in their countries. Nigeria claims that the amount of marihuana smuggling is increasing in West Africa. Togo is concerned about the growing amount of marihuana coming into the country from Ghana and Nigeria.

Mali

Government officials in Mali have stated that the drug problem is beginning to be a serious one in that country, particularly among young people. Large quantities of marihuana and some heroin are being smuggled into Mali, particularly along the Mali-Guinea border. Police and customs officers as well as schools are being mobilized in the fight against drugs.

The Washington Post, in an article datelined April 5, 1970, from Nairobi, Kenya, has this to say about cannabis use in Africa: "Americans tend to think of the smoking of cannabis as a recent and socially dangerous phenomenon, but here in sub-Sahara Africa the use of marihuana is centuries old and African societies show little alarm about it. This may be due to the considerable differences that exist between drug use patterns in America and black Africa. For one thing Africa's young people seem to assert their independence from their parents by not smoking marihuana. The old and the poor have long smoked. And there is nothing daring about turning on since most governments largely ignore marihuana use, although it is illegal in most African countries."

The article goes on to give a few examples of the availability of hemp in various African cities: In Kenya, one can buy a rolled-up newspaper full of marihuana for about five dollars; in Kinshaha in Zaire (formerly the Congo) the going price for a shoebox full of cannabis (called chanvre) is about one dollar.

South Africa

To date, there have been only two studies directly concerned with cannabis use in South Africa and both of them were conducted in mental hospitals. The first of these is a dissertation entitled, The Smoking of Dagga (Indian Hemp) Among the Native Races of South Africa and the Resultant Evils, which was submitted to the University of Edinburgh in 1913 by Charles John George Bourhill for the degree of Doctor of Medicine. The dissertation was based on research carried out between 1908 and 1912 in a mental hospital in Cape Town. (This report continues to be quoted in current government documents on dagga use.) The second study was conducted in 1936 in a mental hospital in Pretoria. It grew directly out of the interest expressed by a Medical Congress meeting in Grahamstown in 1935 in obtaining more factual knowledge concerned with cannabis and its effects.

There are no estimates of use available for South Africa after 1953. In that year, the estimate of users was about 50% of the native male population in some areas but relatively low in others. It is interesting to note that although the phenomenon of acculturation and increasing urbanization have often been associated with a rise in the use of cannabis, many recent South African studies pay comparatively little attention to this phenomenon.

The situation seems to be changing today, however, and there is a general recognition on the part of government officials, academicians, and the general public that the use of dagga deserves a thoroughgoing study. One indication of this is the fact that most observers feel it likely that South Africa will become a party to the Single Convention on Narcotic Drugs before the plenipotentiary conference on proposed amendments to it in March 1972.

In 1969, a committee appointed by the Minister of Social Welfare and Pensions was assigned the task of looking into the whole drug abuse question and issued a full report in 1970, Report of the Committee on Inquiry into the Abuse of Drugs. Unfortunately, the material on dagga is not sufficiently separated out from the material on other drugs of abuse to be able to make any firm statement on prevalence of its use. For example, the committee says, concerning drug use, "It was not possible, therefore, to obtain exact figures anywhere. The phenomenon is far too much of an underground one for that - and this must be emphasized. Although the committee would have liked to obtain exact figures, it realized early on that this would not be possible, anymore than it is possible today to establish the number of people who abuse alcohol or who engage in prostitution. This is not to say, however, that no efforts should be made to do further research on the extent of the problem. So far as South Africa is concerned this field is still unexplored. The Committee recommends that facilities be provided for research on the problem of dependence in all its aspects."

Some observers feel that the use of dagga occurs mainly in cities such as Johannesburg and on the Rand, but others tend to think of it primarily as a rural problem. The probability is that one is dealing with a problem extending along a rural-urban continuum with suppliers and consumers in the rural area and consumers in the urban areas.

The historical record shows that cannabis was used very early in what is now South Africa by the Hottentots and Bushmen -- the first governor of South Africa, Jan van Riebeeck, who arrived in 1652, mentions cannabis smoking, and in the subsequent reports of early travelers there is repeated reference to smoking. Bantu speakers, in fact, smoked cannabis before they smoked tobacco and used the same pipes for smoking cannabis that they now use in some cases for tobacco. Some accounts suggest that the Arabs brought hemp into Central Africa sometime before the Portuguese introduced tobacco.

Another common method of smoking cannabis, still in use in the twentieth century, is to make a clay hollow in the earth where the cannabis leaves (with a small admixture of tobacco) are burnt, and then construct a long tunnel from the hollow to a different spot where the smoker can sit and smoke from a pipe protruding from the ground. Some observers feel that at the present time this method may be in use to avoid the police, however, a variation of this method was in use in the middle of the last century when there was comparatively little danger of arrest.

Some accounts of travelers published before 1850 make it clear that dagga use was not confined to men alone -- an item which is at variance with reports coming from other parts of the world. For example, Arbousset and Daumas, in their *Narrative* published in 1846, give this account of their visit to the Basuto: "The old mamma took from her neck a bit of some narcotic root, lit it at the fire, and bringing it near her nose snuffed in the smoke; while a young matron took from her bosom a small bag of skin containing hemp seed powder of *dagga* and poured out a good dose of it into the hollow of her hand, and there scraped it together with a bit of reed which she had taken from the lobe of her ear where she afterward again replaced it."

Although most accounts speak of the use of dagga through smoking, one traveler, De Grevenboek, writing in 1695, describes another method saying that "they make the roots of Daggha (a plant to which they set great store) into little cakes which they chew, as the Indians do opium, and the Egyptians cetum."

There are well documented accounts to indicate that some of the early settlers cultivated cannabis in order that this could be traded or paid to the Bushmen. This type of trading is not confined to South Africa, of course -- it is strikingly reminiscent of the practice in Peru, common for centuries after the Conquest, in which laborers in the high Andes received part of their wages in coca.

It should be borne in mind that not only the native Bushmen and Hottentots were acquainted with the use of cannabis but also persons who came in from other countries. For example, The Dutch East India Company brought in slaves from the East - a pattern different from that in the New World - and there is evidence that the settlers also cultivated dagga to give to their slaves.

Today Indians are known as the major traders in such places, for example, as Natal. It may well be that usage habits introduced by Indians and Malays have tended to alter some of the indigenous usage habits of the Africans.

There is some historical evidence to indicate that cannabis has been used in at least one part of Africa, as part of an armamentarium of weapons directed against the ruling group - in a manner reminiscent of the use of ganja by the Rastafarians in Jamaica or the early Provos in Holland. It is also strongly suggestive of the introduction of the use of peyote to North American Indians and its continued use among members of the Native American church. (In many of these groups, particularly the Native American church, the stress is put on the use of the drug as an Indian substance as part of an Indian ritual - in contrast to other religious rituals which have been introduced from the outside by white men.)

In Zaire, formerly the Congo, about 1870, among the Luba people, a semi-religious group who called themselves Bena-Riamba, the Sons of Hemp, sprang up. At that time there were no whites in Zaire , and the king was a native. The nation became divided over the question of opening the country to foreign trade. The Sons of Hemp (representing the liberal side) advocated such trade, and the king sided with this party in the end. Opening of the frontiers meant, among other things, that more riamba (cannabis) was brought into the country by Swahili traders from Zanzibar.

The Far East

Japan

Before World War II offenses concerning marihuana were negligible. Immediately after the War there was some use in and around American Army bases, but this use did not spread to any extent. In recent years, however, marihuana use has increased among the Japanese, especially among young adults.

In relative terms the problem is not comparable to that in the United States, since the number of marihuana cases being sent for prosecution went up from only 144 in 1963 to 426 in 1969. However, the Government has taken certain measures to insure that the cannabis use habit is contained. They have instituted a program of destruction of wild growing cannabis, imposed strict supervision of the legal cultivation of hemp for industrial purposes and initiated stricter controls at port areas.

There is strong public support, strict laws and controls, and hospitalization and counseling supplied for narcotics offenders and the program has worked reasonably well. The Japanese are taking a similar approach to control of cannabis use.

Japan has had a great deal of experience in attempts to control the use of illegal drugs. After World War II amphetamines became freely and legally available and usage shot up so fast that it was estimated that about five million Japanese were regular users. In response to this emergency, a highly punitive law was enacted in 1953 against both users and sellers. In 1955 it was considered that the amphetamine problem had been solved, but by this time the number of narcotics addicts had begun to rise. In response to this, the Government (in 1963) passed further laws which were just as stringent as those enacted to control amphetamine use. But as narcotic addiction went down, barbiturate use began to go up and apparently is still rising. In addition, there seems to be a sharp rise in the use of solvents as inhalants.

REPUBLIC OF CHINA

The Government of the Republic of China maintains effective control over the use of narcotics on Taiwan. However, it is concerned over the possibility of increased use of drugs by young people on Taiwan and the problem is receiving increased public and official attention despite present low levels of usage.

The China Post (the English language paper of Taipei) reported on September 30, 1971, that the National Health Administration had announced a total ban on the manufacture, preparation, import, export, sale or display of marihuana, amphetamines and LSD in Taiwan. Marihuana and the amphetamines have been under government control since 1955, but LSD is new to Taiwan.

There are no figures available on cannabis use in Taiwan, but there is some evidence to suggest that some heroin and opium addicts may substitute marihuana or a synthetic drug when their preferred choice is unavailable.

The Ministry of the Interior, in a report prepared for the United Nations in accordance with the International Narcotics Convention, stated that in 1970 there were 1,444 addicts and former addicts registered in Taiwan. Local governments of the Republic of China may turn narcotic addicts over to drug facilities attached to certain public hospitals designated by the government in order to force them to break off their addiction. Police maintain a general roster of addicts. Physicians in public and private hospitals are supposed to notify the police if they find a narcotic addict among their patients in the course of treatment.

There were 1,153 persons arrested in 1970 for illegal possession, smuggling, sale and use of narcotics. About 835 of these arrests were for consumption. The average narcotic user in Taiwan, at least on the basis of the arrest figures, is substantially older than in the United States. For example, out of the 1,153 persons arrested in 1970, almost two thirds of them were over thirty-five.

Taiwan does not produce any narcotics of its own - although there may be a certain amount of home-grown marihuana. Most of the narcotics entering the country are believed to be smuggled in from Hong Kong. Based on customs seizures, morphine, followed by heroin, would seem to be the drug most in demand. Marihuana runs a poor third, with 7.7 grams seized in 1970, as compared to 3,430 grams of morphine and 673 grams of heroin.

Singapore

Historically the drug use problem in Singapore has been a problem of narcotics use, and that to only a minor extent. There is no production, refining or processing of narcotic drugs. Opium use by some old China-born men is decreasing. There is also some use of morphine. Marihuana is used by a few Malays and by some Westernized Chinese youths. Government health authorities have also noted a recent increase in use of amphetamines among students.

There have been some allegations lately that Singapore may be developing into an international transshipment point for drugs to the extent that the government is now considering the organization of a separate narcotics bureau. In addition, Singapore is now preparing to become a signatory to the Single Convention on Narcotic Drugs.

Nepal

Both the production and sale of cannabis and its derivatives are legal, although regulated by law. However, statistics about the amount of cannabis produced and used are fragmentary. It is probably safe to say that, except for religious festivals, the vast majority of Nepalese do not use cannabis or its derivatives.

The use of marihuana varies according to region, religion and caste. In many annual religious festivals cannabis is used and many Hindu ascetics use it regularly. Some Nepalese use cannabis as an ingredient in food, particularly vegetable preparations.

In general, however, use of cannabis and especially its indiscriminate use is frowned upon. To date, the essentially conservative nature of the Nepalese society and the effectiveness of parental and community disapproval has served to keep cannabis use well controlled. If it became necessary to tighten government regulations, most observers believe that the Nepalese would wish to have enough cannabis available to allow for certain religious related usages and to follow ancient tradition.

Korea

Cannabis is illegal in Korea, and there seems to be no current usage among the young -- only among some of the very old. Cannabis is presently used on and around U.S. military facilities in Korea by American personnel.

India

The government excise records of India afford the most accurate statistics on the amount of cannabis used in that country, but it must be recognized that there is no adequate estimate of the amount of material (principally hashish or charas) which enters the country illegally primarily from Nepal.

India makes no attempt to register consumers of cannabis, but it is estimated that the current number of habitual ganja users is about 240,000 (not including the users of bhang or of smuggled charas). This is about one half of the number of licit ganja and charas users (excluding bhang) estimated in 1940. Most observers feel that the steady decline in cannabis use in India can be attributed to several factors including: a reduction in the number of acres licensed by the government for production, higher excise duties, increasing competition from other drugs and a growing belief that cannabis is essentially a low status drug.

At the time of the publication of the Indian Hemp Commission report, Calcutta had the highest cannabis consumption rate of any part of India. Most observers feel that this statement is still true today. In general, the greatest use of the drug occurs in the old princely states and the Muslim areas.

Cannabis is consumed in India in three forms distinguished on the basis of the strength of their psychoactive constituents, and these distinctions incidentally have come to be the standard of measurement used in most parts of the world. These forms include:

1. Bhang - Use of this type, the dried leaves of the plant, is freely permitted throughout the country except that some Indian states exercise limited controls and impose specific taxation. Bhang is widely consumed as a beverage (for medicinal, religious and work adjunct purposes) and in some parts of the country is used more or less as one would use a spice for cooking.
2. Ganja - This stronger type of marihuana is derived from dried flowers and/or fruits of the plant. It is produced legally in only four Indian states. In those states where it is legal, it is stored in state government warehouses and issued to licensed retailers. The Government is committed, under Article 49 of the Single Convention on Narcotic Drugs, to end the use of ganja throughout the country by 1979.
3. Charas (Hashish) - This is the strongest form consisting of resin made from the stem of the plant. This form may not be produced or sold legally in India. It is, however, available in most cities and in some rural areas. Indian government officials report that most of the available charas is smuggled into India from Nepal or Pakistan.

While the government has issued no reports indicating that there has been a rise in the number of cannabis users, there has been an apparent increase in price in urban centers indicating increased demand. For example, in New Delhi hashish or ganja sells for about $67 a kilo while opium retails for $49 a kilo. Some observers feel that this high price for marihuana may not represent increased Indian consumption, but rather the demands of foreign young people who have arrived in large numbers in New Delhi and other major Indian cities in recent years.

Indian authorities do not consider that marihuana abuse is a present or potential social problem, and penalties for illegal trafficking in charas and ganja are much lighter than those applying to opium or psychotropic drugs which the government considers much greater dangers. Under the Dangerous Drugs Act of 1930 penalties for illegal trafficking in ganja and charas extend to a maximum of three years imprisonment, but under Customs regulations or some other provisions of Indian law it is possible that more severe penalties may be imposed.

It should be stressed that marihuana has been and continues to be used in many countries, particularly the underdeveloped ones, for reasons that are different from those of the present day North American user. As late as 1965, for example, a well known Indian author pleaded for the retention of ganja as part of the Ayurvedic armamentarium of Indian medicine, since other more modern drugs were simply not available in the villages. In a current NIMH sponsored study in Jamaica of chronic cannabis users, the researchers have remarked that over and over again they encountered subjects who had never used any other medication including aspirin. Ganja, for them, was an all purpose drug.

Modern observers point to the fact that in India laws against the selling or use of charas are most loosely enforced in cities, such as Calcutta, with the greatest problems of overcrowding, malnutrition and other social ills.

Although there has been an apparent decrease in the overall consumption of cannabis, there is some evidence that India is not immune from the rising use of drugs by students which is characteristic of many other countries.

THAILAND

In October of 1971, the Ministry of Health of Thailand announced a sweeping new program to deal with drug abuse which included: 1) an intensive survey of drug producers, 2) a possible new anti-drug law, and 3) a crash education program. Apparently the concern of the government has been aroused by press reports of the growing use of stimulants and tranquilizers by students and more particularly use by females of a sedative drug called Isonox.

Thailand has long had a problem with opium addiction, especially among elderly Chinese and some of the hill tribes. To the extent that opium derivatives are becoming a problem, most are probably rendered from raw opium produced within the borders of Thailand. High grade white heroin is too expensive for the vast majority of Thai users and there is probably little produced within the country for indigenous consumption. The government has in the past employed extreme punitive measures for the heroin producers who have been caught - including summary execution before a firing squad. These earlier measures seemingly have been effective in reducing the number of heroin producers in Thailand, but many have simply moved their operations to Laos where the laws are much less severe, and to Burma where large wild frontier areas along the border with Thailand and Laos are simply beyond the effective control of the government in Rangoon.

The production of opium was barred ten years ago in Thailand and marihuana production has been illegal since 1934. The illegal production and use of opium has, up until now, been the primary drug abuse problem in Thailand. Most of the opium users are extremely poor and treatment facilities are inadequate.

Vietnam

In 1919 the French authorities prohibited the use, possession and trafficking in opium, certain of its derivatives and marihuana trafficking. In 1966, the United States Bureau of Customs began an advisory program to the Vietnamese government. Although there had been evidence from the beginning of the use of marihuana by U.S. troops, in 1968 the extent of this use alarmed U.S. authorities and several measures were taken in that year to cut down on the production and use of cannabis. The Police Narcotics Section was raised to Bureau Status within the Vietnamese government and the Prime Minister announced more stringent control measures.

In 1969 the Vietnamese government, with financial and technical assistance from the U.S. Bureau of Narcotics and Dangerous Drugs, launched a ground/aerial marihuana hunt and by 1971 had destroyed an estimated half million marihuana plants, mostly in the Delta area.

In December 1969, the government announced the first heroin seizure by the National Police. It was evident, beginning in January of 1970, that heroin had become widely available to U.S. troops and, in addition, that the majority of pharmacies sold amphetamines and barbiturates without prescription.

Throughout 1971, as is well known, the combined efforts of the governments of the United States and Vietnam have been devoted to cutting down on the supply of heroin entering the country, and the Ministry of Health has ordered pharmacies to stop selling dangerous drugs without prescriptions. The U.S. Army has placed all pharmacies off limits. By August 1971, the Government of Vietnam had made 3,974 narcotics arrests and had seized 65 kilos of heroin, 351 kilos of opium, 3,558 kilos of marihuana.

The Government of Vietnam estimates that there are at least 100,000 opium users and 4,000 to 10,000 Vietnamese addicted to other drugs. Plans are underway to establish a treatment center for Vietnamese addicts. It is not possible to tell how many Vietnamese are chronic cannabis users or to what extent this is a problem.

Although police and customs activities have been stepped up, some of these activities have been thwarted since the courts have usually given light or suspended sentences to drug traffic offenders. New legislation, offered by the President in August, is intended to change this since one title in the law states that a convicted offender (except for those over 60 and ill) cannot receive suspended sentences. The new law also spells out, for the first time, clear regulations for the control of amphetamines, barbiturates and hallucinogens.

Cambodia

The existing legislation governing narcotics in Cambodia date from 1955. Narcotics legislation is separate from criminal law. In this legislation, the section covering cannabis is called Infractions of Public Morality. The law provides that the cultivation and preparation of Indian hemp for consumption and commerce is prohibited, and all offenses against this prohibition are punishable by a penalty of the first degree (6 days to one month imprisonment). Anyone who smokes, ingests or provides, for the purpose of smoking or ingesting, Indian hemp is punished by the same first degree penalty. Anyone who furnishes Indian hemp or opium to a person less than 18 years of age is punished by a penalty of the second degree (one month to one year imprisonment).

There are no figures available to us at this writing of the extent of use of cannabis in Cambodia, although based on lightness of the penalties imposed, it does not appear to be seen as a serious problem. The regulations concerning opium use are much more severe.

Pakistan

Pakistan has long had trouble with tribes in its Northwest frontier area involved in the production and distribution of narcotic drugs. People in these remote areas have long made their livelihood from the production of opium and hashish and smuggling, and it is unlikely that they will voluntarily abandon these pursuits at any time in the forseeable future. The development of highly profitable substitute crops would provide an alternative, but such development seems remote at present.

Afghanistan

The government of Afghanistan does not believe there is a drug problem in Afghanistan although there are a number of opium and hashish users. Although the health authorities do not consider hashish to be addicting, use does constitute a social problem since it is used extensively by bus and truck drivers and by many low paid workers in industry. There are no reports of the substantial use of other psychotropic drugs.

Afghanistan encounters difficulties similar to those of Pakistan in dealing with the tribes on its remote frontiers, and a substantial amount of both opium and hashish is smuggled out of the country.

In October of 1971, the government of Afghanistan announced its intention to launch a study of hashish planting and growing practices, about which it has little information at the present time. This study would run concurrently with a second study of the legal and social aspects of hashish consumption and trade. Both studies would be undertaken in order to recommend legislative and enforcement actions at a subsequent date.

The foregoing brief summary of cannabis use in countries other than the United States points up the general inadequacy of the data currently available on the extent, patterns of use, persistence of use, the physical and psychological characteristics of users as well as the general social climate in which cannabis use is either introduced, expands or declines. Research into the relative frequency of the various patterns of cannabis use in varying cultures is needed, particularly research which will probe the therapeutic uses of cannabis in various forms, as well as the use of cannabis as a work stimulant.

The field would profit by studies which would follow a cohort of users in certain selected countries, as well as carefully designed small studies which would examine in depth the natural history of drug using careers. In countries where the use of cannabis is the rule rather than the exception among adult males (Jamaica, for example, where it is estimated that 40 to 50% of the adult males are ganja smokers), it would be profitable to discover how the non-smokers find a role for themselves which is not considered deviant.

In a drug which has such widespread use as well as such a long history of use, it would be useful to have some studies which look into the characteristics of use which were exported from the original country to the countries to which use of the drug was exported along with immigrants. It might also be helpful, in developing countries, to determine to what extent cannabis use is displaced by use of other drugs when cannabis is considered a low status drug.

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V. THE MATERIAL AND ANALYTICAL METHODOLOGY

Plant Material

There seems to be general agreement that the material called marihuana in North America comes from a single species, Cannabis sativa L. However, analytical studies have revealed so many morphological and chemical differences among plants grown from seeds of different varieties that it is probable that the species has not yet stabilized (9). Marihuana consists of a dried mixture of crushed leaves and flowering tops (with or without the inclusion of stems and seeds) of the Indian hemp plant. The plant is an herbaceous annual which grows readily in temperate and tropical climates in many parts of the world and reaches maturation in 4-5 months. Cannabis is usually dioecious, i.e., it has separate male (staminate) and female (pistillate) plants, but some variants have been reported to be monoecious. The flowering tops of the female plant secrete a clear, varnish-like resin which when collected is "hashish." There has been some confusion regarding the word "hashish." Although it is widely used as the designation for the collected resin, in some countries of Africa and Europe it has been used much more loosely and thus it may apply to a concentrated extract or any Cannabis preparation. Publications on hashish do not always clearly specify the characteristics of the material used, such as origin, type (pure resin or others), source (confiscated or collected under controlled conditions). This eventually leads to confusion and makes it difficult to compare data between different laboratories.

Contrary to previous beliefs, all the parts of the plant, including the leaves, contain psychoactive principles (cannabinoids). There is now convincing evidence that these cannabinoids are present in male as well as female plants (39,15). However, in a given plant, the cannabinoids are most abundant in the flowering tops and the bracts, the young, small leaves surrounding the seeds. The percentage of active principles per dry weight of plant material decreases in the following order: bracts, flowers, leaves, smaller stems, larger stems, roots and seeds (15). Using a scanning electron microscope, Fairbairn recently demonstrated that the cannabinoids are not restricted to the glandular hairs as was usually assumed, but are also present in "sessile glands" (12). Typical stalked glandular hairs were found in large numbers only on the bracteoles and at the base of the small bracts subtending them. However, on the other leaves, which contained cannabinoids and where no glandular hairs are present, he noted the presence of numerous large spherical sessile glands, which function as excellent storage containers for cannabinoids. These glands were found intact in the carefully air-dried plant after two months of storage at room temperature.

This variation in the percentage of active principles between the different parts of the plant emphasizes the importance of the mode of preparation of marihuana. A carefully "manicured" sample containing mostly flower tops and bracts will be more potent than another sample from the same lot which contains mostly leaves and a high percentage of stems.

To insure standardization of samples distributed for research, marihuana grown under contract by the National Institute of Mental Health (HSM-42-70-109) for distribution to researchers is always passed through a 10-mesh screen, eliminating most of the stems and seeds. This marihuana comes from different batches of various composition (low and high THC content) and is blended to insure a standard percentage of cannabinoids, usually 1.5-2% Delta-9-tetrahydrocannabinol.

Chemical Composition of Cannabis

The composition of Cannabis is quite complex. It is only recently that availability of modern separative and analytical techniques has allowed researchers to isolate and elucidate the structure and absolute configuration of the active principles of Cannabis. Two reviews of its chemistry are quite current (31,38).

Cannabis constituents are divided into two major classifications: the cannabinoids, which contain most of the active principles, and the non-cannabinoids including waxes, starches, terpenes, oils and traces of other identified or non-identified materials. Among the non-cannabinoid materials, twenty-three monoterpenes, the volatile constituents of fresh marihuana, have recently been identified by a gas chromatography method using a capillary column (1).

Other identified non-cannabinoidal materials, such as alkaloids and nitrogenous bases (25,45) are found in such small amounts in the plant that their importance, in terms of the total effect of marihuana on health remains to be demonstrated. For many years a mixture of unidentified tetrahydrocannabinol isomers was assumed to be responsible for the activity of Cannabis (48). It was not until 1964 that the isolation and structure of the active constituent of Cannabis, the Delta-9-tetrahydrocannabinol, was described by Gaoni and Mechoulam (18). In a recent publication (19), these authors review the full details of their work on isolation and elucidation of the structures of Delta-9-tetrahydrocannabinol (the major active component of marihuana) and of three minor cannabinoids: cannabigerol, cannabichromene and cannabicyclol. Extraction of confiscated hashish "soles" (at least one year old) with petroleum ether showed that there are at least four principal groups of related chemicals present in the resin of the plant .
The first of these, the aromatic fraction, contains a single chemical, cannabinol (CBN); the second group is represented by the presumably active components, the tetrahydro-derivatives of cannabinol of which there are at least two: the Delta-9- and the Delta-8-tetrahydrocannabinols (Delta-9-THC and Delta-8-THC);the third group contains the two-ring resorcinol analogs known as the cannabidiols (CBD); the fourth group contains the carboxylic analogs of the

above three. The first three groups are found in the neutral fraction of the petroleum extract, the last group, the carboxylic acids in the acid fraction. The amount of neutral cannabinoids found in various samples of hashish is indicated in Table 1. In these hashish samples, Mechoulam could not detect Delta-8-THC, the isomer of Delta-9-THC. The presence of this tetrahydrocannabinol in marihuana has been reported by others, but the ratio of Delta-8-THC to Delta-9-THC varies from 1:10 (50) to 1:100 or even lower (29). Part of the problem in quantifying the amount of Delta-8-THC lies in the difficulty of making a good separation by gas chromatography between the Delta-9- and Delta-8-THC peaks, as these compounds have very close retention times.

The structure of Cannabidiol (CBD) was elucidated before that of the Delta-9-THC. Re-investigation of the photoreactivity of CBD has shown that irradiation of CBD in cyclohexane led to cyclization of CBD to Delta-9-THC (43). Although the same authors have proposed CBD as a precursor of Delta-9-THC in the plant (31), they do not believe this reaction to be of any importance to explain conversion of CBD into THC. If such a reaction did in fact take place, intermediates would be found which have never, so far, been isolated from natural sources (43). CBD is always present in the plant in detectable amounts and there seems to be an inverse relationship between the amounts of Delta-9-THC and cannabidiol present in the different varieties. This finding led Waller, Doorenbos,

TABLE I

Content in Hashish of Some Natural Neutral Cannabinoids (19)

	% Yield in Various Samples
Cannabidiol	3.74 (1.4) (2.5)
Delta-9-THC (Delta-1-THC)	3.30 (1.4) (3.14)
Cannabinol	1.30 (0.3) (1.2)
Cannabigerol	0.30
Cannabichromene	0.19
Cannabicyclol	0.11
Delta-8-THC (Delta-1,6-THC)	Not detected

and their group to classify Cannabis sativa varieties into two chemical "phenotypes" according to cannabinoid content; the drug type and the fiber or hemp type (52,8). The drug type has a high percentage of Delta-9-THC and the ratio Delta-9-THC+CBN/CBD is greater than 1. The hemp type contains a higher percentage of CBD and the ratio Delta-9-THC+CBN/CBD is lower than 1.

Until 1963, the only cannabinoid with a fully known constitution was cannabinol (CBN). It is present in hashish and in some samples of plant material (Brazilian) in sizeable amounts (greater than 1%). It seems to increase with the age of the sample as Delta-9-THC is converted to CBN.

Recently new constituents of hashish have been identified and found in sizeable amounts in some samples of hashish of eastern (Pakistanian) origin (50, 19a, 35,51). These compounds are tetrahydrocannabivarin, cannabidivarin and cannabivarin, the propyl homologues respectively of THC, CBD and CBN. These homologues possess a propyl C_3H_7 side chain instead of a C_5H_{11} amyl side chain. They are reported to be present in such sizeable quantities (15.8%, 5.7% and 12.3% respectively for cannabivarin, tetrahydrocannabivarin and cannabidivarin) that they may influence the biological activity of the hashish samples. Although tetrahydrocannabivarin has been shown to be five times less potent than Delta-9-THC in the catalepsy test in mice devised by Paton , it is more polar than tetrahydrocannabinol, and this characteristic may influence resorption, onset of action and formation of polar metabolites in man. Using sophisticated gas chromatography-mass spectrometry methods, Vree et al., in addition to the propyl derivatives, identified methyl analogs of Delta-9-THC and CBN in a Brazilian hashish sample and the methyl side chain analog of CBD in a Lebanese sample. They have named these side chain methyl analogs: Delta-1-tetrahydrocannabiorcol, cannabiorcol and cannabidiorcol (51).

Nomenclature

Adding to the complexity of marihuana chemistry, two different nomenclatures are presently used with about equal frequency by the various investigators, based on the dibenzopyran or the monoterpene numbering systems. Depending on which one is used, the major active component of marihuana, for instance, is called either Delta-1-THC or Delta-9-THC. As new metabolites and cannabinoids are discovered, the problem has become extremely complex. However, there is some hope that a solution is near and that a universal nomenclature may be adopted. At a recent (October 25-28, 1971) Cannabis Symposium in Sweden, a resolution was drafted, signed by most of the scientists presently engaged in Cannabis research, and sent to the President of the International Union of Pure and Applied Chemistry (IUPAC). In this resolution, the researchers asked IUPAC to make a final decision on the universal nomenclature to be adopted and agreed to then use the recommended nomenclature.

Structure Activity Relationships in the Cannabinoid Series

While few cannabinoids have been tested in humans, the structural requirements for activity in the monkey are being unravelled (32,33,10). As summarized by these authors using the monoterpenoid nomenclature, they are as follows:

1. A benzopyran-type structure with a hydroxyl group at the 3' aromatic position and an alkyl group on the 5' aromatic position seems to be a requirement. Opening of the pyran ring leads to complete loss of activity.

2. The aromatic hydroxyl group has to be free, or esterified. Blocking of the hydroxyl group as an ether inactivates the molecule.

3. Substitution on the phenolic ring with alkyl groups at $C_{4'}$ retains activity. Substitution at $C_{6'}$ eliminates activity. Electro-negative groups such as carboxyl, carbomethoxyl and acetyl at either $C_{4'}$ or $C_{6'}$ eliminate activity.

4. A certain length of the aromatic side chain is a requirement for activity. Branching of the side chain may lead to considerable increase in potency. The 1,2-dimethyl-heptyl side chain seems to be optimal.

5. The terpenoid ring may apparently be amended considerably. It seems that substituents on C_1 and C_2 have to be in the plane of the ring (i.e., equatorial) in order that high activity be retained. A double bond in the terpenoid ring is not a requirement. While

Delta-1 and Delta-6 THC's (in the 3R, 4R series only) are active, Delta-5 is inactive; Delta-3 is active; Delta-1-THC (3,4-cis) is inactive.

Using the behavioral monkey test, Mechoulam found that Delta-9-THC is the major active component of Cannabis. The acidic fraction of the petroleum extract of marihuana containing carboxylated derivatives of the major cannabinoids was found to be inactive. However, these acids are found in a very high proportion in the fresh plant and they are decarboxylated by smoking, in storage or by gas chromatography to produce the neutral cannabinoids. These acids are very labile compounds and difficult to isolate (40). Lack of practical synthetic methods for producing these acids in good yields has so far prevented further evaluation of their biological effects.

Structure activity relationships in a series of synthetic tetrahydrocannabinols (Adam's compounds) had also been thoroughly investigated after intravenous administration of these compounds to anesthetized and unanesthetized dogs more than fifteen years ago, but results have only recently been declassified and submitted for publication (24). It was found that the two synthetic tetrahydrocannabinols which were the most potent were the dimethylheptyl (DMHP) and the methyloctyl (MOP) derivatives. Both had a double bond in the 6-A-10A position of the A ring with an aliphatic side chain in the 3 position of the B ring of the dibenzopyran structure.

Methodology Used to Test Cannabinoids

In view of the great number of chemical compounds found in Cannabis sativa, it became necessary to develop accurate methods to quantify these components and to test their biological activity.

A. Bioassays

They are mostly qualitative or semi-quantitative. Originally two bioassays were used: the rabbit corneal arreflexia test developed by Gayer and the dog ataxia test . More recently, Paton developed a catalepsy test in mice (41a) and Truitt (48a) has developed a series of behavioral tests which can be used as an experimental model of marihuana effects. However, some of these tests require large doses of compounds which produce neurological deficit and may reflect pharmacologic effects of Cannabis without direct correlation with the psychoactive effects observed in humans at much lower dose levels. The semi-quantitative test developed in monkeys by Edery and Mechoulam has been used to study structure activity relationship in the cannabinoid series. A major advantage of this test is that the threshold dose for effective compounds, such as Delta-9-THC, is about 500 micrograms/kilograms. which is about in the same dose range as demonstrated for psychoactive effects in man (10).

B. Analytical Methods

An excellent review of the state of the art in the analysis of marihuana has been recently published (44). Before considering the analytical procedures per se, it is important to discuss the methods for preparing the samples for analysis.

a. Preparation of Extracts. The main cannabinoids are essentially neutral and non-polar compounds, and petroleum ether and hexane have been the solvents of choice for their extraction (19). However, ether has been used recently to extract some of the more polar metabolites (28). Samples of human and animal origin are handled somewhat differently. In serum, direct extraction with heptane, followed by evaporation under reduced pressure, has been used (28). After incubation, the samples are then extracted with petroleum ether, concentrated by evaporation and subjected to analysis.

b. Analytical Methods. Color tests such as the Duquenois-Levine test and the Beam test have been routinely used over the past several decades as chemical tests for the qualitative identification of marihuana. The Beam test has the advantage of being fairly specific as only two plants (rosemary and salvia) and one chemical gave faintly positive results in tests of over 200 plants and chemicals. But the disadvantages of this test are its lack of sensitivity and the fact that it only measures cannabidiol and does not give a positive reaction with Delta-9-THC. The Duquenois test is more sensitive than the Beam test but can also give false positives. The danger of false positives with the color tests and the microscopic tests has recently been pointed out by Fochtman et al. (16). These investigators found out that products as widespread as coffee and spice substances may interfere with chemical tests such as the Duquenois-Levine test. They recommend that further identification be made by thin layer-(TLC) or gas liquid-chromatography (GLC). Therefore, to increase accuracy, it has become generally accepted that these color tests should be performed in conjunction with a microscopic test for physical identification and with a TLC or GLC test for quantitative evaluation of the various cannabinoids (5). Microscopic identification must be carried out by experienced personnel since numerous other plant materials can be confused with marihuana because of similar microscopic appearance (37). For many years, paper chromatography was the method of choice for determining the relative concentrations of the various cannabinoids in marihuana. It has now been replaced by thin layer chromatography and gas liquid chromatography.

In most of the recent papers, Fast Blue B (Naphtanil Diazo Blue B) has been used as the reagent to develop the color of the various cannabinoids on thin layer plates (44). The TLC techniques can be divided into three major systems. One system employs plates of silica gel impregnated with dimethylformamids and uses cyclohexane as an eluent. It has been used to analyze plant extracts (26) and to determine cannabis metabolites in urine (6). Others employ silica gel-silver nitrate plates to determine the various cannabinoids (21) in plant extract. Many different solvents were used but benzene (49,44) seems to give the best results. The limit of sensitivity appears to be on the order of 0.05mg for THC with this method. Finally, others used untreated silica gel plates and a mixture of solvents (31,28). Mechoulam uses a solvent mixture of pentane and ether to determine cannabinoids in plant extracts and Lemberger a mixture of hexane and acetone to study THC and its metabolite in human serum, urine and feces.

c. Gas Chromatography is now extensively used for the analysis of Cannabis extracts and in most cases effective separation of the major components has been obtained. Analyses can be done by injecting an appropriate aliquot of the extract directly into the gas chromatography and determining the constituents by their retention times. Direct combination of gas chromatography with infrared spectrophotometers and mass spectrometers (51) and indirect combination with paper chromatography and TLC have been used in identification of many of the constituents of marihuana. The difficulty encountered in using the gas chromatograph alone in identification of samples is that only one parameter of a compound, its retention time is being determined. Another difficulty is that the carboxylic acids of the cannabinoids, present in the fresh plant, are automatically decomposed at the GC analysis temperatures and do not give a peak. This has the advantage of giving the total cannabinoid content which is absorbed by smoking, for instance. But it is a disadvantage if knowledge of the components as present in the fresh plant is required. For these reasons, Paris, using densitometry after separation by TLC, has developed a new test for quantitation of cannabinoids, especially the acids (41,13). TLC also has been used to detect compounds which have very different retention times from the main cannabinoids and therefore can be missed by GLC (34). These problems with GC can be at least partially resolved by the formation of derivatives, such as trimethylsilyl and fluoracetate and methylated derivatives.

The formation of trifluoroacetic, trichloroacetic (36) and heptafluorobutyric derivatives of THC or of its metabolite allows the use of the increased sensitivity of an electron capture detector and may lead to the gas chromatographic determination of the THC metabolites in biological samples.

A new method of centrifugal chromatography which has provided rapid qualitative analyses of components in extracts of marihuana and hashish may also prove valuable for the quantification of cannabinoids in the urines of marihuana smokers (42).

So far it has not been possible to quantify cannabinoids in human biological material except by using radiolabelled materials and counting the radioactivity. In order to avoid administering radioactivity to humans, attempts have been made to use fluorescence analysis for the determination of THC by making highly fluorescent derivatives with either maleic acid or dansylated derivatives (3,17). Unfortunately, these methods are not yet sensitive enough to detect the very small amounts of cannabinoids present in the plasma of marihuana smokers.

Another innovative approach is also being pursued by various laboratories, i.e., the development of an immunoassay for detection of marihuana in biological fluids . Antibodies generated by a Delta-9-THC azo derivative have been found to react with native Delta-9-THC. Fluorescence quenching of antibody and fluorescence enhancement of haptene provided quantitative standard curves in neutral aqueous solutions (20). It is probable that a workable procedure for THC immunoassay will be established within the next six months. The question remains: will it be specific enough to discriminate between cannabinoids and their metabolites or will it be only a rapid detection test which must be complemented by GLC to obtain discrimination between the various cannabinoids?

Impurities and Mislabelling of Plant and Synthetic Material

In addition to the complex question of the chemical composition of Cannabis sativa L., which has been treated in some detail in the previous section of this report, the issue of impurities (additives, diluents and contaminants) in plant material and mislabelling or false claims made about plant or synthetic material must be considered. Currently, little is known about either aspect as it affects physical and psychological reactions.

Conceptually, three major questions exist:

> What is the nature of the problems of impurities and mislabelling in marihuana plant material and synthetic cannabinoid compounds? How frequently do these problems occur and what patterns or correlates exist with regard

> to impurities and mislabelling?
>
> How important is the absence of systematic quality controls of illicit marihuana? Do impurities and mislabelling have harmful consequences for health?
>
> How does this question affect other areas, either directly through the need for treatment of adverse reactions, educational efforts, performance of chemical analysis of suspected specimens or indirectly by contributing in some measure to all aspects of the marihuana problem?

Marihuana from street sources, as compared with standardized material, has more variable levels of Delta-9-THC and is typically of rather low potency. Therefore, most naive users and many experienced users have difficulty detecting the absence of active ingredient and the presence of substituted material. Testing of leaf material by sight or sensation is unreliable. Many substances resemble marihuana well enough to confuse users as to their identity oregano, tea, catnip, parsley, rosemary, lawn grass, etc., are commonly found in specimens claimed to be marihuana. Whether used as a substitute, filler, cutting agent or adulterant, the material is often given away or sold without knowledge of the buyer-receiver. The degree to which mislabelling occurs is limited only by the audacity of the dealer-giver and the naivete of the buyer-receiver.

No reliable evidence has been found to support the existence of "synthetic grass" on the street, although speculation about its availability goes back several years. Capsules, powders and tablets have been sold and consumed in the belief that they were "synthetic marihuana;" in many cases the drug has turned out to be phencyclidine hydrochloride, commonly referred to as PCP or the "peace pill." A possible reason for this is that with synthetic, verification of contents is even more difficult than for plant material.

The issue of impurities and mislabelling of plant and synthetic material affects research, education and treatment. Plant material used in early marihuana research was not only varied in per cent Delta-9-THC concentration, but some of it contained other substances, such as fatty acids not usually present in the plant. Some of the doubtful results of early research may have been due to this. At the present time, we are unaware of any studies which are employing additives in deliberate fashion to determine how responses may be affected.

The question of impurity has direct bearing on drug education efforts. In a recent article on the contents of illicit drugs(46) Smith stated:

> The use of the impurity issue to give clout to educational efforts is welcomed by those who have employed traditional health education with questionable results.
>
> Educators and mass media personnel should be cautious in their use of the contaminants issue and not involve it without supporting evidence. Exaggerated claims and a new mythology about contaminants will only set back or undercut honest efforts to inform people about drug contents and effects. The fact that many young people appear to be more willing to accept this type of information makes it more important to proceed cautiously.

The question of the relationship of the contents issue to treatment is complex since at present the number of persons requiring treatment because of marihuana use, with or without additives, is unknown. Addition of adulterants may modify a symptom picture or in themselves cause adverse reactions which then may be incorrectly attributed to the marihuana itself.

A dearth of published studies exists in this area. It is known that there are several programs around the country and in Canada that provide drug analysis as a service for the community, parents, treatment agencies and drug educators. The coordination of these programs, including the collection and analysis of data obtained in each, would be of valuable service to the community.

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VI. PRECLINICAL RESEARCH IN ANIMALS

PRECLINICAL STUDIES IN ANIMALS

This section summarizes a wide range of investigations in animals that are designed to learn some of the implications of Cannabis administration in man. Progress has been significant this year in the toxicology, metabolism, neuropharmacology and behavioral areas.

Most of the earlier information on the pharmacologic actions of marihuana in animals and man was concerned with the behavioral effects of Cannabis extracts which were usually of undefined potency and were given in unknown amounts. This made it extremely difficult to interpret much of the animal research on marihuana prior to 1964 when the active principle of marihuana, the Delta-9-THC, was isolated. With the availability of pure compounds and of dosage forms of known composition, reports on the neurophysiological and biochemical, as well as behavioral, effects of Cannabis are now rapidly appearing. During the last two years a number of books (53,31a), reports (33,44) and reviews (7,36,47,58,25), and symposia (three in the United States, three in Europe) have summarized and considerably clarified the preclinical effects of Cannabis. Publication of these conferences is in progress.

In the toxicity area, studies in animals have shown that the margin of safety between the lethal doses and the pharmacologically active doses of cannabinoids is large, and that Delta-9-THC and

Delta-8-THC could be safely administered to man for Phase I and early Phase II clinical studies.

Research on the metabolism of marihuana in animals has shown that cannabinoids disappear very rapidly from the blood, and that metabolites are formed which remain in the body for a long time. A great number of metabolites have been found in vivo and in vitro but their possible relation to the psychoactive effects of marihuana remains an area of important investigation. This hopefully will be accomplished in FY 73 when practical syntheses for these new compounds are developed, making available sufficient quantities of these metabolites for controlled clinical and preclinical studies. It is well established now that the effects of the tetrahydrocannabinols on the central nervous system are complex and that these compounds show a mixture of stimulant and depressant properties.

As the synthetic Delta-9- and Delta-8-THC have become available in larger amounts through the NIMH drug supply programs, investigators have been able to study the chronic and the acute effects of the tetrahydrocannabinols. Chronic studies have shown that different behavioral patterns develop after repeated daily administration of the same dose for one month and more, and that tolerance develops rapidly to some of the effects of the tetrahydrocannabinols. It should again be emphasized that the dose levels frequently employed in animals (to test the limits of toxicity, for instance) are often much higher than those used by humans, and that the methods of administration may be substantially different. Nevertheless, preclinical testing is essential for an understanding of the mechanism of action of a drug and for developing useful clues to fruitful lines of investigation in man.

Solvents and Routes of Administration

To appreciate the difficulties involved in preclinical marihuana research, it must be remembered that the cannabinoids are thick, non-crystallized, water insoluble compounds. Because of this extreme insolubility in water, the administration of pure cannabinoids in animals is very difficult and requires the addition of such materials as emulsifiers, suspending agents or solubilizing vehicles which may have pharmacologic effects of their own.

Research on development of suitable agents for administration of Cannabis in chronic studies was carried out under NIMH contract. It was found that the best solvent for an oral preparation (with a concentration of THC greater than 1%) is sesame oil. Stock solutions of THC in sesame oil were found to be stable for months, and could be used directly for oral administration or for formulating injectables (51). Suitable emulsions for parenteral use could be obtained by dispersing THC in various agents, such as in sesame oil (51) Tween 80 in saline (50), polyvinylpyrrolidone (15), plasma lipids (12), bovine serum albumin (45,25), lipaemic serum (5). To alleviate the irritant effects of organic solvents, a water suspension has also been proposed for intraperitoneal injection of Delta-9-THC. However, the compound precipitates out when it comes in contact with metal (48,49). Comparing the acute effect of Delta-9-THC in four different vehicles on the same pharmacological end-point, Sofia et al (55), showed that absorption from the peritoneal cavity depends on the solvent used, and that a suspension of 10% propylene-glycol and 1% Tween-80 in saline seems to be the vehicle of choice for THC administration by this route. Delta-9-THC suspended in 1% Tween-80 saline or in bovine serum albumin-saline was not absorbed from the peritoneal cavity.

The route of administration has proven to be critical in determining the quantity of cannabinoids absorbed and their effects. For chronic studies, the oral route of administration seems to be the preferred route. Although it is not the usual route of self-administration of marihuana in man, quantitative comparisons of dose levels can be made between oral and smoking studies. Even though some primates can be taught to smoke, this is not a convenient way to administer marihuana chronically. Smoking devices (masks) have been developed but the smoke is mostly inhaled through the nose by the animals in a manner different from that in man. In addition, in smoking studies it is difficult to accurately measure the dose administered in the absence of quantitative tests for the determination of cannabinoids in blood and plasma.

The intraperitoneal and subcutaneous routes of administration should definitely be avoided in chronic studies. Although measurable pharmacological and behavioral effects do occur after intraperitoneal administration of relatively large doses, autoradiographic studies (27,28) have shown that radiolabeled Delta-9-THC administered intraperitoneally remains in the abdominal cavity, with little absorption and distribution to other tissues such as the central nervous system, while the same dose given intravenously or by inhalation was distributed rapidly throughout the body (26). In other studies, 30-day intraperitoneal administration of either Delta-9-THC or a marihuana extract produced chronic diffuse chemical peritonitis, lesions and abscesses in muscle, subcutaneous tissue and skin of the ventral region of rats (55). In the same study, rats treated orally or with vehicle controls did not show these changes. Dose-related dermal irritation and granuloma formation was also noted in rabbits after 30 days of daily subcutaneous administration of Delta-9-THC.

TOXICITY STUDIES

Acute Toxicity

Recent availability of sufficient quantities of pure Delta-9 and Delta-8-tetrahydrocannabinols and of a marihuana extract of well defined composition has permitted systematic studies of the acute and chronic toxicity of marihuana and synthetic cannabinols. These new studies have confirmed previously reported observations (37) that huge single doses of cannabinoids could be administered to various animal species by the oral or intraperitoneal routes of administration without causing death. Single oral doses of Delta-9 or Delta-8-THC as high as 525 mg/kg in dogs and 1,050 mg/kg in monkeys were non-lethal (57).

Comparison of the acute toxicity of Delta-9-THC in rodents (mice and rats) by three different routes of administration (i.v., i.p., oral) has shown that Delta-9-THC was 20-30 times more toxic when given intravenously than when given orally. Given i.p., it is about 10 times less toxic than given i.v., but slightly more toxic than when given orally (49,57). The LD 50_s in rodents (lethal doses in 50% of the animals) were 20-40 mg/kg for i.v., 400 mg/kg for i.p., and between 700 mg/kg to 1,400 mg/kg orally, depending on species and sex.

In higher species (dogs and monkeys), it was not possible to obtain an LD 50, but the minimal lethal dose was about 1 Gm/kg orally.

This lack of toxicity may have been partially due to poor intestinal absorption. When a comparison study was done in which the three compounds (Delta-9-THC, Delta-8-THC, and extract) were given orally or intravenously in 3 species (rats, dogs and monkeys), Delta-9-THC was found to be more potent than Delta-8-THC. Death was rapid (within 5 minutes) after intravenous administration, and delayed from 10-72 hours post administration when the cannabinoids were given orally (57 ,48). By the oral route, Delta-9-THC is more toxic to female than to male rats (56). The response in animals after oral administration of the pure compounds and of Cannabis extracts are very similar to those in animal smoking experiments. These signs include hyper-motility, muscle tremors, hyper-sensitivity to sound and sedation. Hyper-reactivity to stimuli is more marked in monkeys than in dogs. The monkeys also exhibit a characteristic huddled posture that has been used as an end-point for characteristic marihuana activity.

Death is usually preceded by severe hypothermia, ataxia, stupor, loss of righting reflex and dyspnea progressing to apnea.

Chronic Toxicity

This year, for the first time, the results of repeated administration of cannabinoids over periods of time ranging from 30 to 119 days were reported. In interpreting the results of these chronic toxicity data, one must remember that, in subacute and chronic toxicity studies, the doses administered, although smaller than in acute studies, still are much larger than the psychoactive human doses. For instance, the human oral dose of marihuana which produces psychoactive effects in man varies from 200-500 microgram/kg. Thus, a 50 mg/kg dose in animals is about 100-250 times greater than the effective human dose.

In view of the high doses needed to produce toxicity in animals with cannabinoids and the large quantities of compounds needed for these experiments, toxicity studies have had to be limited in time. The longest toxicity studies have been performed under contract with the NIMH and lasted 119 days. Oral doses of Delta-9 and Delta-8-THC (50-500 mg/kg) and marihuana extract were given to rats. It was found that cannabinoids exhibited a bimodal pattern of toxicity. Initial changes indicated a dose related generalized depression similar to that observed in animals treated acutely. This initial depression was manifested as inactivity, slow movements, wide stance, weight loss, hypothermia and hypopnea. Approximately 72 hours after the initial treatment, the rats started to exhibit tolerance to these depressant effects and became more active. This enhanced activity was manifested as increased exploratory behavior, grooming, and motor activity. Later, these rats became hyper-irritable, exhibited fighting and had to be placed in separate single cages to avoid further wounding of cage mates (56). As the hyper-irritability increased over time, tremors and later clonic convulsions occurred in increasing numbers of animals. A similar increase in aggressiveness was previously reported in chronic studies by Carlini, but in animals which were food deprived (10).

Drug-related histopathological changes observed at autopsy included hypocellularity of bone marrow and spleen and vacuolization and hypertrophy of the adrenal cortex. In monkeys, some tolerance to depression followed by hyperactivity was noted but it was less marked than in rats.

Initial weight losses and significant decrease in the rate of weight gain were reported by many authors. The peak for this effect occurs within 2-8 days after the first administration. After a week, the animals resume gaining weight but at a lower rate than control groups. This effect on body weight gain has been correlated by some with a decrease in food consumption (43). Others have not found such a correlation (56).

A 28 day subacute toxicity study was also conducted in monkeys given Delta-9-THC by the intravenous route at doses of 5, 15, and 45 mg/kg/day (14). Fifty per cent of the animals in the high dose group died in the middle of the study as a result of acute hemorrhagic pneumonia. Behavioral, clinical and hematological changes were similar for monkeys treated with single or 28 daily doses and included dose related sedation, huddled posture, bradypnea, hypothermia, bradycardia, weight loss, constipation, anemia and increased BSP retention. These effects increased over a period of days, but tolerance eventually developed. The delayed deaths, indicative of cumulative toxicity, and the appearance of edema, ulceration and fibrosis at injection sites in the cannabinoid treated groups (but not in vehicle controls) were the major toxicological differences between the single and 28 daily treatments.

Teratology (Preclinical)

The effects of marihuana on pregnancy and the newborn are still under debate. Except for a report in the "lay" press (18) of teratology defects in the second generation of rats subjected to marihuana smoke, no additional data on teratology of marihuana has been reported this year. Evaluation of this report, which so far has not been submitted for publication in the scientific literature, is difficult as the investigator used marihuana from confiscated supplies of unknown origin and the complete methodology has not been described. These studies are now being replicated by the same investigator using marihuana of standard composition.

As this question is of primary importance in considering the effects of marihuana on health, a number of NIMH-supported studies are currently under way to explore possible teratological aspects.

Metabolism (Preclinical)

During the past year, studies on the metabolic fate of cannabis constituents have exerted a pronounced influence on the course and shape of marihuana research. This area has been surveyed recently (59, 35), as the rapid accumulation of metabolic data has made a summary of the current status of metabolic studies desirable. Preclinical research in this area is particularly important as it offers clues which could not be obtained in humans to the absorption and distribution of cannabinoids.

New data confirming the chemical structures of the tetrahydrocannabinol bio-transformation products such as 11-hydroxy-Delta-8-THC, 11-hydroxy-Delta-9-THC, 7,11-dihydroxy-Delta-8-THC, 8,11-dihydroxy-Delta-9-THC, and other derivatives has been very helpful in explaining the time course and activity of the drug. The importance of the 11-hydroxy-THC derivatives as direct-acting metabolites in producing the effects of THC on the brain has been of particular interest. Also, the fact that non-specific oxidases in the microsomal portion of liver cells produce the initial hydroxylation steps explains the interaction of marihuana with many other drugs metabolized by these same enzymes. Knowledge of the chemical structures of the dihydroxy-THC and other further transformation products (such as acids) may shortly produce a basis for chemical determination of the presence of the drug in urine and feces of the users.

Undoubtedly, further research will yield a multitude of additional products, but these derivatives account for the bulk of the persisting radioactivity.

Marihuana metabolism research can be divided into the phases of absorption, distribution, metabolism and excretion. All of these interact and influence one another, especially when the drug is chronically administered. The high lipophilicity of THC determines many of its characteristics of uptake and biotransformation, while the more polar nature of the metabolites predicts their excretion patterns.

a. Absorption

Although marihuana is usually smoked in this country, preclinical investigators have typically used other routes of administration, such as intravenous, intraperitoneal and sometimes oral administration. These routes produce a more quantitative and convenient form of drug delivery even though they are different from street use. Although smoke inhalation is almost comparable to intravenous injection in rapidity of action, a certain percentage of the compound is lost by smoking. There is still controversy about the quantity lost in this manner. Foltz et al (17)

found that about 50% to 60% of the drug is lost during pyrolysis, but other studies have found a still lower percentage delivery (14-20%).(2) These variations in delivery rate are probably attributable to differences in experimental design and to such other factors as the length of the butt ("roach") remaining after smoking and the rate and temperature of combustion. Shown in Figure 1 is a diagram indicating the distribution of Delta-9-THC in a machine-smoked reefer ("joint") when a 25% butt was saved.

As mentioned previously (see section on solvents and routes of administration), other routes of administration give lesser efficiency and slower onset of effects. Doses to produce comparable effects to the I.V. route in animals are about three times higher for oral and five to ten times greater for intraperitoneal acute administration. Very poor absorption occurs following subcutaneous application and i.p. administration.

b. Distribution

A number of laboratories have now confirmed the very rapid disappearance of THC upon its absorption into the circulation. This appears to be due to its rapid conversion to 11-hydroxy-THC and to a high rate of uptake by neural and other lipoidal tissues. After a rapid phase of decline of THC in plasma for the first one to two hours, a slower rate of decrease is seen and lasts for several days after a single administration (34,35).

In the plasma, the lipophilic THC is transported mainly in association with lipoproteins, whereas the more polar metabolite 11-hydroxy-THC is bound to albumin.

DISTRIBUTION OF Δ^9-THC IN MARIHUANA SMOKE

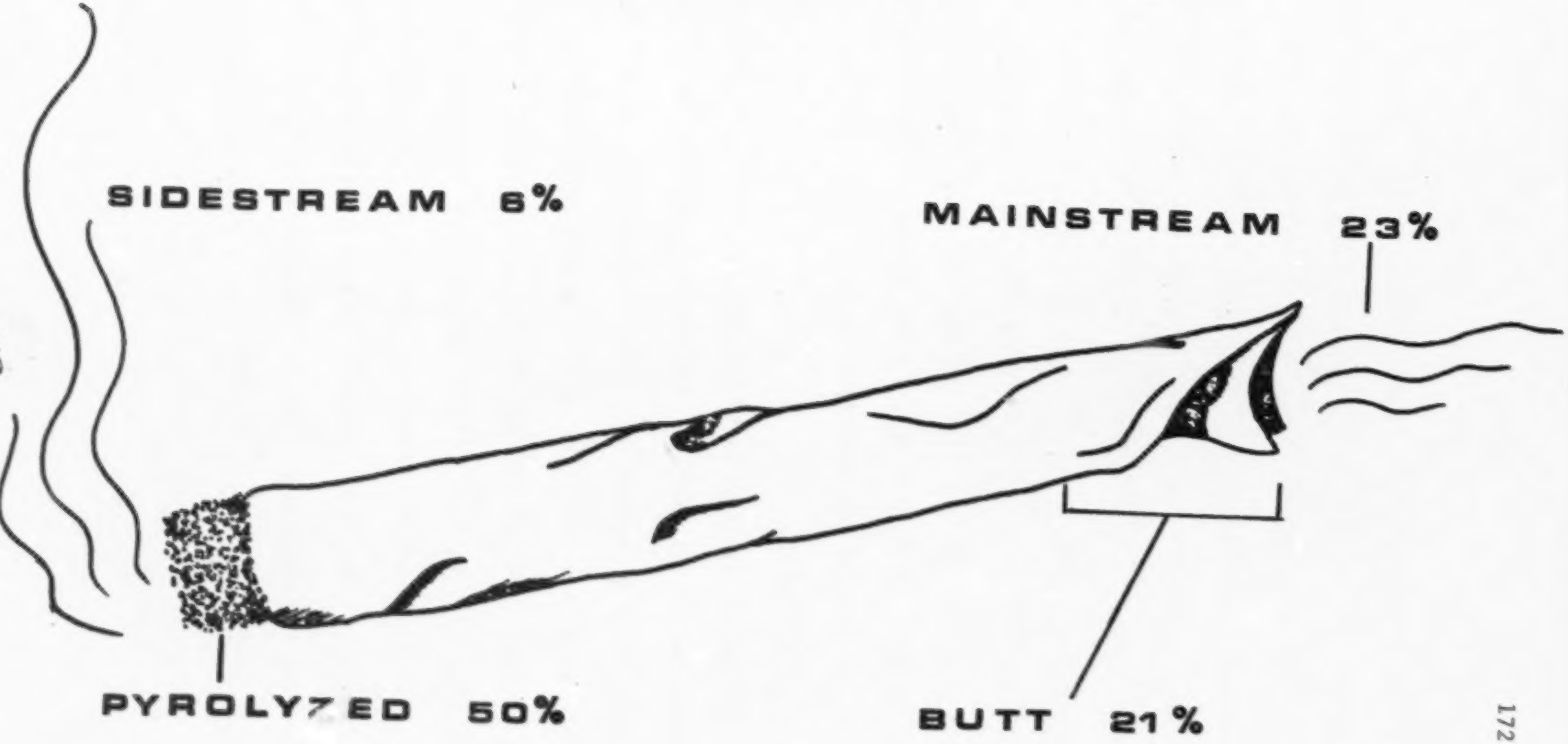
SIDESTREAM 6%
MAINSTREAM 23%
PYROLYZED 50%
BUTT 21%

Figure 1.

The initial distribution of the drug is primarily governed by the vascularity of the organ involved with the brain receiving a large amount very early. Other organs showing high levels at this time are the liver, spleen, lung, heart and kidney. The pattern of distribution is not significantly different when smoke inhalation is compared to the intraperitoneal route, except for the initial retention by the lung following smoking (26).

A special case of drug distribution is that of pregnant animals. It has been shown that THC crosses the placental barrier and may produce sizeable concentrations in the fetus (31,24[20]). The significance of this transfer of THC to the viability of the fetus is being investigated by current projects.

A later phase in the disposition of THC in the body involves the redistribution of the drug from the organs of high early concentration to those involving excretory function. Thus, later time periods (after sixty minutes) show high concentrations of the drug in the liver, bile, gastrointestinal tract, kidney and bladder. These organs are involved in the metabolism and excretion of the drug. An unusual aspect of THC metabolism is the recirculation of metabolic products which proceed from the liver via the bile duct and gall bladder into the gastrointestinal tract, where they are re-absorbed and secreted again in an entero-hepatic circulation (32). Two other organs which retain excessive amounts are the spleen and adrenal glands. Such concentrations may result in toxic changes in these areas as shown in rats receiving large doses chronically.

The special case of brain distribution of THC and its metabolites has received attention during the past year (40). High brain levels of the drug persist about as long as in any other organ. Although the rat brain does not show marked differences in area distributions, the monkey brain shows an early concentration of the radioactive drug in the grey matter rather than the more lipophilic white matter, especially in the visual and frontal cortex (40). Further studies by this group has shown that the high affinity for the frontal and visual cortex areas is due to a metabolite rather than THC itself (40). The behavioral significance of this uneven distribution remains to be established, although the implications of these areas for explaining the memory (frontal cortex), ataxic (cerebellar) and emotional (hippocampal and amygdaloid areas) are quite obvious.

c. Metabolites

One of the most significant early findings in the metabolic research on marihuana has been the discovery of 11-hydroxy-THC as a direct-acting metabolite (17,61,4). Further studies have now appeared showing that there is a rapid conversion of Delta-9-THC to 11-hydroxy-Delta-9-THC in the liver (32) and in the lung (46a). A correlation has been made between brain levels of this metabolite and rat cataleptic (trance-like) behavior (23) and in humans between euphoria and plasma levels (34).

The most important aspect of the participation of the $NADPH_2$ and O_2 non-specific oxidases located in the microsomes of liver cells in the progressive hydroxylation of THC is the fact that many other drugs are metabolized by these same enzymes. However, they are seldom converted to an active form as is the THC. Thus it is now possible to explain an interaction of THC with barbiturates that can be through metabolism changes as well as neural synergism. Many drugs which are also metabolized by microsomal enzymes such as anti-coagulants, anti-diabetic drugs, anti-depressants, tranquilizers, analgesics and others should also be examined for their interactions with THC.

Further oxidations of Delta-9-THC beyond the stage of 8,11-dihydroxy-Delta-9-THC remain uncertain and need confirmation. A metabolite hydroxylated on the amyl side chain has been reported (61, 1). An acidic metabolite has been found in urine but its exact nature and conjugation will require further study (8). This metabolite, because it accounts for such a large portion of the excreted form of THC, may be useful in developing chemical tests of Cannabis usage.

d. Excretion

The principal routes of excretion for Cannabis metabolites are through the feces and urine. The relative amounts of metabolites excreted via these two avenues vary from species to species. The rat resembles man in having a large proportion of the metabolites excreted in the feces. This is apparently a reflection of the higher activity of an enterohepatic recirculation in these species in contrast to rabbits, for instance.

The most important characteristic of the excretion pattern is the long persistence of radioactive metabolites for days or even weeks following a single large dose in animals and man. Because of this the use of Cannabis will be detectable for a longer period than that of alcohol once an analytical determination of the metabolites will be established.

In summary, studies in the metabolism of Cannabis have provided many insights into the nature of marihuana action. These include the identification of its active moiety, the persistence of its effects and a possible explanation of tolerance reflecting both the initial decrease and later an increase at higher dose levels.

Central Nervous System Effects

During the past year, additional evidence indicating both a depressant and a stimulant effect of cannabinoids on the central nervous system (CNS) has been obtained. As mentioned previously (toxicity section), single doses produce dose related CNS depression but continued administration over long periods of time (over a month) show stimulatory effects. This mixture of depressant and stimulant effects may be related to the observations that Delta-9-THC increases barbiturate sleeping time as well as potentiates the stimulatory effects of amphetamines.

An explanation of the mechanism of action of cannabinoids will have to take into account their effects on brain biogenic amines.

An upsurge of papers appeared during the past year dealing with the effects of pure THC on brain biogenic amines. Two groups have reported that THC produces a rise in brain serotonin (5-hydroxyptryptamine, 5-HT), in animals, but authors have disagreed about whether the rise was confined to the forebrain (62) or to the hypothalamus (54). The rate of 5-HT turnover was also reported to be decreased.

A slight drop in norepinephrine (NE) brain levels reported by Holtzman et al (30), has not been confirmed by other groups (22,62) However, by measuring the turnover of radiolabeled H^3-NE, several groups have noted significant effects on this biogenic amine. Schildkraut et al, for instance (52), have shown slight increases in turnover rate, metabolism and uptake of norepinephrine. The endogenous levels of NE were slightly decreased while those of 5-HT were slightly higher than controls. The effects of THC on norepinephrine seem to differ with the mode of administration. If THC is given before the radiolabeled compound, there is an increased retention of tritiated norepinephrine (H^3-NE) (59), or an increased uptake by brain slices (21). When the radiolabeled H^3-NE is equilibrated with the brain first, THC causes an initial acceleration of NE turnover (41,27), but the drug has no effect when applied to slices removed from the brain, possibly because of an inability to form an active metabolite (21). Using fluorescence methods two groups have found that THC ingestion increases the fluorescence of localized brain areas particularly the hypothalamus. This increase in fluorescence is believed to be correlated with an increased concentration of catecholamines in these areas (46). These findings suggest that THC has marked effects on NE as well as 5-HT. Studies in this area are highly preliminary. Much further work is needed to clarify the effects of THC on brain biogenic amines and to compare THC to other psychoactive drugs.

Evidence of increase in DNA in rat brain after administration of Cannabis resin had been previously reported (9) and was confirmed this year at high dose levels of THC (38). This may be part of the neurochemical mechanism involved in the production of short-term memory loss in man by marihuana which has so often been reported in the literature.

The basic neurophysiological and neuropharmacological mechanisms of marihuana effects are still unclear. However, some comparisons between barbiturates (pentobarbital) and Delta-9- and Delta-8-THC indicate that the tetrahydrocannabinols are quite different from barbiturates in their effects on the polysensory areas of the cortex. These areas are important since they may be involved in an overall integration of sensory information. An increased responsiveness of cortical areas produced by THCs without the concomitant decrease of recovery produced by pentobarbital has been found by Boyd (6). This effect may be related to the changes in sensory perception caused by the tetrahydrocannabinols.

A number of new reports appeared this year regarding the electroencephalographic (EEG) effects of marihuana compounds. Confirmation of the appearance of high voltage slow waves in the EEG of awake animals came from various studies (13 , 30 , 3). This disruption of the normal waking EEG correlated with changes in behavioral pattern and was reported to be present even at low dosage levels of cannabinoids. These EEG related effects have been reported for some hallucinogens such as psylocybin and Ditran. It is noteworthy that the EEG effect is produced by a dose of THC (0.5 mg/kg) quite similar to that which has been found to be hallucinogenic when smoked by humans.

Research in a number of laboratories is now focusing on the effects of THC on specific brain areas, such as the hippocampus, the septal area, and the hypothalamus, which are known to be involved in psychoactive effects or body regulatory functions. By autoradiography, McIsaac et al (40) found accumulations of the drug or its metabolites in the lateral geniculate nuclei, the amygdala, hippocampus, and inferior and superior colliculi of the brain at the time of maximal behavioral activity in the monkey. Large concentrations in the cerebellum may also relate to the incoordination and ataxia observed following large doses.

Behavioral Effects

The behavioral effects of the tetrahydrocannabinols were extensively reviewed last year (44). The need for evaluation of the behavioral effects after repeated, chronic administration is now recognized, because it has been shown that behavioral effects after long-term chronic administration are different from those observed after acute administration.

Behavioral studies have been made using observational methods or operant behavior methods. The effects of Delta-9-THC on aggressive behavior is still under debate. A number of studies have reported an effect on aggressiveness but depending on the dose, the time after drug administration and the nutritional state of the animal, aggressiveness can be either enhanced (10,11,56) or decreased (31b).

To study its abuse potential, self-administration studies have been performed. So far, it has been found that animals do not self-administer Delta-9-THC. Experiments are continuing in that area using various methods to see if animals can be induced to self-administer THC.

Operant behavioral methods have been used to study the effects of THC in a number of species. At behavioral dose levels, most studies have demonstrated a drop in work output even on simple tasks requiring very little effort (16). No evidence has been found of a "reverse tolerance" in animals but most studies have indicated that behavioral impairment is most severe after the initial administration and tends to decrease thereafter. Behavioral effects are under study in various laboratories using monkeys and chimpanzees. In these species, as contrasted to rodents the effects of marihuana are seen at dose levels comparable to those at which psychoactive effects are seen in humans.

Cardiovascular and Autonomic Effects

The tetrahydrocannabinols present unique profiles of cardiovascular and autonomic effects.

It has been shown in most clinical studies that Delta-9-THC produces a dose-related increase in heart rate when smoked or taken orally by man, and that this increase is the best physiological index of THC activity. Cardiovascular studies in anesthetized dogs have shown that the intravenous administration of comparatively larger doses of Delta-9-THC produced a prolonged bradycardia, and that this bradycardia was accompanied by a pronounced hypotension of long duration (up to 7 hours) (14a). As barbiturates used for anesthosia have been shown to interact with cannabinoids , these experiments were repeated this year in unanesthetized animals under acute and chronic treatment with Delta-9-THC. It was then found that Delta-9-THC initially produced bradycardia in about half of the dogs tested. Tolerance then developed, and at higher dose levels the bradycardia was changed to tachycardia on approximately day 6 or 8 of treatment. There was no significant change in blood pressure in these unanesthetized dogs after either acute or chronic administration (14a). Therefore, the hypotensive effects previously reported in animals (and not usually observed in man) are probably the result of an interaction with the barbiturates used for anesthesia.

Delta-9-THC has been shown to have a specific effect on respiration. A single dose of 5 mg/kg, i.v. in anesthetized dogs, produced an increase in rate associated with a decrease in depth of respiration and produced a state of hypoxia in spontaneously breathing animals. This resulted in a decrease of arterial PO levels. However, no alterations in the blood gas parameters were observed in artificially ventilated animals (11a).

Studies on the mechanism of the cardiovascular effects of Delta-9-THC indicate that cardiovascular responses to THC *in vivo* may be partly due to a direct action of the drug on heart contractility (3a). Central or peripheral (vagolytic) autonomic mechanisms may also be involved (7a ,59a).

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VII. TOLERANCE

TOLERANCE

The question of presence or absence of physical dependence and tolerance to marihuana has become quite important and was the subject of several investigations during the past year.

Physical dependence is defined as the existence of a characteristic abstinence syndrome produced by withdrawal (discontinuation) of the drug. Evidence for such an abstinence syndrome with Cannabis is weak. From both Eastern and Western clinical reports and from animal experiments there seems to be agreement that physical dependence comparable to that produced by the opiates, alcohol, and barbiturates does not exist with Cannabis. Although some reports have described mild, brief symptoms in patients who discontinued Cannabis use (11,4,24) these seem to be insignificant and cannot be easily differentiated from possible placebo effects.

The core of the controversy therefore centers around whether or not tolerance develops to marihuana and its constituents. Tolerance to a compound is said to have developed "when after repeated administration, a given dose of a drug produces a decreasing effect, or conversely when increasingly larger doses must be administered to obtain the effects observed with the original dose" (12). As noted recently by Kalant (14), this definition of tolerance is valid only for a specific drug action and not necessarily for all the actions of a given drug. A definition of tolerance should also discriminate between metabolic tolerance and functional tolerance. Metabolic tolerance includes those changes in drug absorption, distribution, excretion and metabolism which might lead to a reduction in the intensity and duration of contact between a given drug and its "target" tissue. Functional tolerance refers to changes in the properties and functions of the target tissue which render it less sensitive to the same degree of exposure to the drug. So far, most of the reports of tolerance to marihuana effects have attempted to explain the huge tolerance discovered in terms of metabolic tolerance. According to modern concepts, the degree of tolerance should also be evaluated at different dose levels to establish a dose response curve. This might give some clues on the mechanism of action of the development of tolerance. The use of a single test dose at an unknown point in the dose response curve may explain some of the controversial findings about tolerance to marihuana.

In man, the reports on tolerance to marihuana use are so far contradictory. A number of reports in the Eastern literature have described the use of very large amounts of cannabis by chronic users (5,7). These amounts are much larger than doses which cause considerable dysphoria in less experienced subjects who are given the drug on an experimental basis. The fact that the chronic users tolerate these doses well and are able to continue their usual activities suggests development of tolerance to the subjective effects of the drug. However, others report that even use for many years does not necessarily cause increase in doses.

Some authors, commenting on reports that many first or second time users of marihuana report no subjective effects, have suggested a "reverse tolerance" in which with increasing use the subject acquires the ability to get high (25).

Two investigations which compared effects of administered marihuana in experienced and casual users have indicated that experienced users have greater sensitivity to the subjective effects of the drug, but show less decrement in perceptual and psychomotor performance (22,28). Thus, there may be different patterns of tolerance for the different pharmacological effects of the drug. Jones and Stone found that heavy users could not significantly discriminate between THC-containing and THC-free cigarettes although physiological effects such as altered pulse rate and EEG changes in the subjects were good indicators they had received the active compound (13).. They also found some evidence of cross tolerance with alcohol. These last experiments seem to confirm one of the main tenets of marihuana mythology that experienced users get "stoned" more readily than do the inexperienced. Thus marihuana has been reported to produce a "reverse tolerance" in that a smoker becomes more responsive with repeated use and needs less of the drug for similar effects. As mentioned by Snyder (26), this effect of marihuana, if confirmed, is a peculiar and disquieting state of affairs for the pharmacologist. Indeed, in experiments with drugs which are capable of inducing tolerance, the subjects usually become less and less responsive to each successive dose of the drug and the dose must be increased to obtain similar effects.

Several factors may have contributed to the conflicting findings regarding development of tolerance in man after marihuana use. For instance, as tolerance to a drug is often defined only in terms of a diminishing response to a constant dose, failure to control the dose adequately may make demonstration of tolerance difficult. Early investigators had to use marihuana of varying composition rather than pure compounds. The methodology and the criteria used by investigators to assess tolerance and to define the various types of users (naive, casual and experienced) were not rigidly controlled. As mentioned previously, tolerance may be due to learning or metabolic changes. Lemberger et al have shown that heavy users of marihuana seem to metabolize Delta-9-THC more rapidly than non-users (16). If some or all of the psychological effects of Delta-9-THC were due to an active metabolite then enzyme induction with more rapid conversion of the Delta-9-THC in heavy users might well explain this phenomenon.

Further confirmation of the presence or absence of tolerance in man will be obtained when the results of the current subacute and chronic studies in man are reported.

In animals, since the report of tolerance in rats by Carlini in 1968 (3), development of tolerance after repeated cannabinoid administration is now well recognized and documented. Some confusion still exists about the type of tolerance observed (behavioral only or pharmacologic) and the type of pharmacological effects which show tolerance versus those which do not.

In an excellenct description of the characteristics of tolerance based on preclinical data, McMillan et al (19) have reviewed this complex phenomenon and have defined the following criteria for tolerance to marihuana:

1. Tolerance to marihuana extends across species. It has been demonstrated in birds (pigeons) as well as in rats (3,8,19,20,27), dogs (19), monkeys (27), chimpanzees (6,9) and to a lesser degree in the mouse. The only species in which tolerance to cannabinoids does not seem to develop is in the rabbit (17). This may be due to a different metabolism of tetrahydrocannabinol in this species. Agurell (1) has shown that, in rabbits, the principal route of excretion is through the urine rather than through the feces as in rat and man.

2. This tolerance develops rapidly and may be long-lasting. Various authors have shown that tolerance develops rapidly in pigeons, dogs and rats (19 27,8) even when the injections are spaced seven to nine days apart. They also found evidence that tolerance to THC in these species is persistent. There is little loss of tolerance to a high dose of Delta-9-THC even after a month. However, Pirch _et al_ found that the interval between administrations was a significant factor in the development of tolerance in rats and that daily administration of the same dose of a marihuana extract produced tolerance, although weekly administration does not (23). This seems to demonstrate that animals treated with low doses of marihuana, in the behavioral range, return to their control baseline within a few days after a single administration.
3. The magnitude of tolerance development to marihuana in animals is great. It is reported to be in excess of one hundred fold, i.e., one hundred times an initially effective dose produces little effect in tolerant dogs and pigeons. The same authors have also shown that this tolerance can be blocked by SKF-525-A, an enzyme inhibitor which may interfere with the metabolism of Delta-9-THC (19).
4. Among the cannabinoids, there is cross tolerance between Delta-8- and Delta-9-THC and between Delta-9-THC and its synthetic analogues. But there is no cross tolerance between Delta-9-THC and LSD or mescaline sulfate. Tolerance development to the tetrahydrocannabinols differs from tolerance development to morphine; a narcotic antagonist disrupts behavior in morphine-tolerant birds, but not in Delta-9-THC-

tolerant birds, and cross tolerance between Delta-9-THC and morphine could not be demonstrated by McMillan et al in pigeons (20).

5. Tolerance to tetrahydrocannabinols is not simply a result "learning to respond under drugs", i.e., a behavioral tolerance, but a true pharmacologic tolerance in that the lethal dose is also increased during tolerance development. Tolerance can develop even when the animals are not exposed to the schedule contingencies on all the days when injections are given.
6. Finally, development of tolerance seems to be specific for certain effects of the cannabinoids and not for others. This may explain some of the contradictory results regarding tolerance. It has been shown, for instance, that in dogs tolerance develops to the hindleg ataxia but not to anorexia and sedation (19).

In separate experiments in rats, Barry and Kubena did not observe development of tolerance. In one experiment, they showed facilitation of an avoidance response and in the other elevation of plasma corticosterol levels by Delta-9-THC. In both experiments, there was no dimunition of these effects after repeated administration of daily doses (2, 15).

Pirch et al (23), confirming the early results of Masur and Khazan (21), observed no tolerance in rats to the induction of bursts of "polyspikes" during 30-35 days of treatment with a marihuana extract. However, they found tolerance after two days to the generalized reduction in cortical EEG voltage in the same animals.

Development of tolerance to an effect of the cannabinoids may unmask or help the development of the opposite type of effect. This type of biphasic action has been recently reported. Lomax (18) found that the first daily injection of 20 mg/kg of Delta-9-THC in rats produced significant hypothermia but after the sixth daily injection hyperthermia was seen. Thompson et al have shown that tolerance develops to the sedative effects of the cannabinoids but not to their stimulant effects (27). Conceivably, the euphoria occurring after administration of Delta-9-THC to man could be classified as a "stimulatory effect" to which tolerance does not develop. Indeed, repeated administration could result in increased sensitivity to these effects as tolerance developed to others.

In summary, tolerance to the effects of the tetrahydrocannabinols is a unique pharmacological phenomenon with wide generality and many interesting features. Its mechanism of action is currently under investigation in various laboratories, and should be elucidated in the very near future.

Long-term experimental studies which monitor a number of the pharmacological effects of marihuana on humans are needed. It seems, however, unlikely that in man a degree of tolerance comparable to that found with opiates exists with marihuana.

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VIII. EFFECTS IN MAN

Acute Effects

Acute Physical Toxicity

Chronic Physical Effects

Genetics and Birth Defects

Cannabis and Psychiatric Illness

Acute Effects

The acute effects of marihuana intoxication vary considerably due to several factors which can be classified as related to the marihuana itself, the dose and route of administration, the individual's rate of metabolism, his past experience with the drug, his expectations as well as the environmental and social setting in which the intoxication takes place.

As synthetic trans-delta-9-tetrahydrocannabinol (henceforth referred to as THC) has become available (mainly through the national marihuana program of NIMH), it has been possible to study the basic chemistry and pharmacology of marihuana and to obtain the first data on the human metabolism of this psychoactive ingredient of marihuana. These will be discussed in the next few sections in detail. The role of expectations and setting are best discussed in relation to the endpoint of the effects studied, i.e., the physiological, biochemical, neurological, cognitive, psychomotor and subjective aspects.

The Question of the Active Ingredient

There is no doubt that the major active ingredient of marihuana, as far as the typical euphoriant effect in man is concerned, is Delta-9-THC (59,67,95,96). At least most of the psychological effects of marihuana can be reproduced by the administration of synthetic Delta-9-THC. There are, however, other ingredients in marihuana that may play a role in its biological activity. In freshly harvested marihuana there are comparatively large amounts of cannabinoid acids which are rapidly converted when heated, and slowly when stored, into decarboxylated neutral cannabinoids, including the active Delta-9-THC (95). Delta-8-THC, which occurs in much smaller concentration than Delta-9-THC, is also active (5) but no detailed analysis of its psychological effect in man is available as yet (61).

It has been suggested that cannabidiol, occurring in variable but sometimes significant concentration in marihuana may be converted to Delta-9-THC during smoking (101), but this suggestion needs confirmation.

The psychotropic activity of the other ingredients of natural marihuana, whether neutral (cannabinol, cannabigerol, cannabicyclol, cannabichromene, etc.,) acidic (cannabidiolic acid, cannabinolic acid, cannabichromenic acid, etc.) or alkaloid (82) has not been investigated (95). It is quite possible that some of these materials have psychotropic or biological activity different from that of Delta-9-THC and may play a role either in modifying the effect of Delta-9-THC or producing some side effects. Further research comparing the natural material with the synthetic THC is under way to shed some light on this problem (41,104,131).

Dose and Route of Administration

There are two major ways of consuming marihuana: smoking and oral ingestion. When smoked, THC is rapidly absorbed and effects appear within seconds to minutes. If marihuana is of low potency, effects may be subtle and brief (139). Seldom do they last longer than 2 to 3 hours after a single cigarette, although users may prolong the effects by repeated smoking (59). When the material is smoked, an uncertain and variable fraction of THC is lost by smoke escaping into the air or exhaled from the respiratory dead space. Investigators, in trying to control this variable have adopted either a standardized routine of inhaling, holding the breath and finishing the cigarette within a given period of time (81), or using a spirometer to deliver the smoke and bringing the time variable of inhalation under stimulus control (113).

Since no method for the quantitative estimation of THC concentration in blood or urine is available by conventional chemical techniques, radioactive labeled THC has been used to obtain such data. C^{14}-labeled Delta-9-THC was administered to chronic marihuana users by the smoking route by Galanter *et al*. There was a marked variability in the amount of Delta-9-THC absorbed. This was reflected both in plasma concentrations and in urinary excretion of the tracer (extractable by heptane and consisting mostly of unchanged Delta-9-THC). From these data it was estimated that the percentage of THC absorbed can vary between 15 and 41 percent (43) in contrast to the earlier estimate of about 50% absorption based on using a mechanical smoking device to imitate human smoking and measuring the delivered THC in the smoke (91). These data suggest that quantitative comparisons across subjects in studies of smoked marihuana must be made with extreme caution.

Oral ingestion usually delays the onset of the psychological effect for from 30 minutes to over 2 hours (63). The effects peak at approximately three hours and have a duration greater than four hours (87). This delay occurs because synthetic THC, as well as marihuana extracts, require nonpolar vehicles, usually alcohol or vegetable oil. These apparently delay the absorption of the THC from the gastrointestinal tract (63). The importance of the vehicle for the rate of absorption from an oral dose of labeled material for three oral vehicles - alcohol, sesame oil and aqueous glycocholic acid solution - has been demonstrated by Perez-Reyes and Lipton (107). It was found that THC in doses of 37 mg. (total dose) is very poorly absorbed from an alcoholic solution as indicated by: 1) A low plasma level of total radioactivity; 2) a large portion (70%) of radioactivity recovered from the feces in the first 3 days after administration; 3) slow onset and relatively moderate intensity of the psychological effects.

In contrast to this result, THC was absorbed much better from sesame oil solution and even faster from the glycocholic acid preparation of THC. This was evidenced by high plasma levels, lower recovery rate of radioactivity from feces, and faster onset with higher intensity of the psychological effects after administration in these vehicles. These subjects also reported much more unpleasant experiences than they did after receiving the same dose of THC in an alcoholic vehicle. This may explain why Hollister et al (63) were able to administer doses of 70 mg. of Delta-9-THC dissolved in ethanol to subjects without the unpleasant effects that Perez-Reyes' subjects experienced when the drug was administered with the other two vehicles at half that dose (107). The maximum safe and tolerable dose of Delta-9-THC in the sesame oil vehicles has been found to be about 40 mg. by other investigators as well (40).

Metabolism of Delta-9-THC

With the availability of radioactively labeled Delta-9-THC, the major active ingredient of marihuana, it has been possible to overcome the analytical difficulties and to begin investigating the problems of marihuana metabolism in humans.

Lemberger et al (86) have compared the metabolism and disposition of C-14-Delta-9-THC in non-users and chronic users of marihuana after intravenous administration. Plasma levels of the unchanged drug declined rapidly during the first few hours after administration, but after this rapid initial decline, Delta-9-THC disappeared from plasma at a slower rate in both groups. The plasma half life for the unchanged drug was significantly shorter in chronic marihuana users (28 hours) than in the non-marihuana-smoking subjects (57 hours). It appears likely that this difference is the result of an increased rate of Delta-9-THC metabolism in chronic marihuana users. This group of subjects excreted in the urine significantly greater percentage of the drug as metabolites in the first two days than did the non-user group (86).

Delta-9-THC has been found to be almost completely metabolized in man (84). Less than 1% of the intravenously or orally administered dose can be recovered unchanged from the urine or feces. Up to one third of the metabolites can be recovered in the urine, and one half to two thirds can be found in the feces, regardless of the route of administration (87). Using various extraction procedures, and thin-layer chromatography at least 5 or 6 metabolites can be separated (107). Of these, only three have been identified so far. A minor but probably psychologically active metabolite is 11-hydroxy-Delta-9-THC, and another, probably inactive metabolite, is the 8,11-dihydroxy-Delta-9-THC (25). A third, major metabolite is probably a 7-carboxylic acid derivative of Delta-9-THC (135), and several other, so far unidentified, metabolites appear to be polar compounds of acidic nature (85,135).

The question whether or not the psychological activity resides in the unchanged Delta-9-THC or in the 11-hydroxy metabolite has remained controversial. Lemberger et al (87) have compared the peaks of the psychological effect of C-14 labeled Delta-9-THC after oral and inhaled administration with plasma levels of the drugs and its metabolites. Good correlations were found between the time course of the psychological effects and plasma levels of radioactivity. They both peaked at 10 to 30 minutes after inhalation and at approximately

3 hours after oral administration. It is not clear, however, whether the radioactivity in plasma represents unchanged THC or some of its metabolites since all are included in the radioactivity measured. In a separate study by Galanter et al (43) plasma levels of unchanged Delta-9-THC were compared with various parameters of the effect of the drug after administration by the smoking route. It was found that only the heart rate increase correlated with that of plasma Delta-9-THC concentration, and that the other, mostly subjective, symptoms of the marihuana "high" appeared and dissipated more slowly.

In a collaborative study by Perez-Reyes (107) and Wall (135), labeled Delta-9-THC was given orally to volunteers and the plasma samples were analyzed for detection of the level of unchanged drug as well as that of the various metabolites. They found little unchanged THC at the peak of the psychological "high", but various amounts of the metabolites were present in the plasma with high individual variability. Obviously, much more research is needed to clarify the role of metabolism in the various effects of THC and marihuana in man.

Subjective Effects of Marihuana and THC

The subjective effects of marihuana intoxication are highly variable since a number of non-drug factors can markedly influence the potential effects at any given time. Since the laboratory situation allows for the study of only a limited range of subjective sensations, Tart (128,129) undertook an extensive survey to explore the total range of potential effects under conditions of ordinary marihuana use. After a preliminary paper in Nature (128) which was quoted in the first Marihuana and Health Report (93) the full details of the survey were published in book form (129).

The reports of 150 experienced marihuana users, estimated to cover the effects of about 37,000 occasions of use, were analyzed to discover the common and characteristic subjective effects of marihuana in non-laboratory settings. Perception of the external environment is changed in practically all sensory modalities. With respect to vision, characteristic effects reported are: seeing forms, and meaningful patterns in visual material that normally is ambiguous, and finding visual imagery more vivid than usual. For hearing, the awareness of subtle qualities of sound, i.e., purity, distinctness and rhythms, is one of the most characteristic effects reported. The subjective enhancement of the non-dominant senses, such as touch, taste and smell is very common. The perception of the space/time matrix normally serving as a background for sensory perceptions is radically changed in marihuana intoxication. This is probably related to changes in time perception - slowing down, even stopping of time - which are most striking. Interpersonal relations are also changed by marihuana to such a degree that many users feel it is a social drug par excellence. It appears, however, that the drug acts as a potentiator of social interaction at low or moderate levels of intoxication only. At higher levels, marihuana may have an opposite effect, making the user less social and more withdrawn from group interaction, apparently because of the great intensification of inner experience.

The effects of marihuana on memory and higher mental processes have been extensively studied by several investigators using well controlled, objective techniques. Their results will be discussed in a later section. The effect of this drug on emotions is highly subjective and difficult to measure. In Tart's sample of subjects the most characteristic effect on emotional mood reported was an almost invariably pleasant, positive emotional state. However, occasional "freak outs," that is, temporarily overwhelming negative emotions occurred in 20% of the users. In this study in only one case was the disturbance serious enough to require professional assistance; in others, the disturbance subsided with reassurance and support of friends. We have to keep in mind that because of the types of subjects selected (users who chose to continue to use) the negative, unpleasant effects are probably underrepresented, as the author himself indicates (128).

The attitude and expectations of the subject and the social setting are important determinants of the subjective effects produced by marihuana (137,142). Jones, in a double-blind study (70) using a single active dose of marihuana (9 mg. Delta-9-THC) and a dose of placebo cigarette, has shown that many subjects rate their subjective level of intoxication after smoking placebo identically to that after smoking marihuana. Prior experience with the drug and an over-learned set of expectations appear to be important determinants of this placebo effect.

In another set of experiments, Jones (71) compared the subjective scores of a group of subjects after smoking the same dose of marihuana in a group and in a solitary setting, using the same laboratory room. In the group setting, subjects experienced significantly more symptoms in three of the four clusters of subjective scales. A greater variety of symptoms were also reported in the group situation, while in the individual test situation predominantly sedative effects were reported. These results suggest that the interpersonal situation and the subjective expectation can be just as important in determining the subjective effect of marihuana as the dose of Delta-9-THC in the smoked cigarette (71).

Kiplinger et al (81) demonstrated that if the set and setting are kept constant, and the Delta-9-THC is delivered in individually calibrated cigarettes, the subjective response of subjects (naive and occasional users of marihuana) will be significantly related to the dose of Delta-9-THC. The subjective response in this study was quantified by using scores from the Cornell Medical Index and the Addiction Research Center Inventory. The authors also measured Delta-9-THC-produced changes in motor performance, mental performance and physiological phenomena which will be discussed in the following chapters.

Physiological Effects

The two most consistent physiological effects of marihuana, an increase in pulse rate and reddening of the eyes, have been described in last year's Marihuana and Health Report and have been confirmed and further studied by several independent investigators (43,81,113).

Perhaps the most consistent physiological occurrence after smoking marihuana or oral administration of pure samples of Delta-9-THC is an increase in heart rate (64,67,139). Kiplinger _et al_ (81) demonstrated that the heart rate increase was dependent on the dose of THC administered and appeared to have a time course with a peak at 20 minutes and a gradual return to normal or near normal by 85 minutes after smoking. The average increase in heart rate for the 15 subjects after the highest dose of marihuana (Delta-9-THC=50 μg/kg) was 23 beats per minute. Galanter _et al_ also found a very early peak, an increase of about 40 beats at 15 minutes after finishing smoking the marihuana cigarette (containing 10 mg. of Delta-9-THC). This rate returned to normal in about 1 hour (43). An average increase of approximately 20 beats per minute was reported by Renault _et al_ (113) at the highest dose (435 mg. marihuana - approximately 6.5 mg of Delta-9-THC) of their dose-response study. No differences were observed between experienced and inexperienced smokers in this measure. Attempts were also made to elucidate the mechanism by which marihuana produces this consistent effect. Experiments using the Valsalva maneuver suggested that marihuana may have its effect on heart rate by altering normal autonomic tone (113). Pretreatment with a beta-adrenergic blocking agent, propranolol, prevented the increase of heart rate with marihuana, indicating that this effect is probably mediated through a beta-adrenergic autonomic mechanism (15).

Johnson and Domino (69) in studying the cardiovascular effects of marihuana smoking with the help of electrocardiograph recording confirmed the time course of the heart rate increase and that it is dose-related. Systolic and diastolic blood pressures were significantly elevated only after relatively high doses (smoking more than 10 mg. of THC), but blood pressure was better correlated to heart rate than to dose. Changes in the electrocardiogram were minimal. Premature ventricular contractions were observed in only 2 of 15 subjects receiving 10 mg. or more of THC but this effect was more likely to be related to smoking than to the pharmacological effect of THC. Since similar cardiovascular changes can also be produced by nicotine and caffeine in susceptible individuals, the clinical significance of the finding with marihuana is probably no greater than that for susceptible subjects smoking tobacco and drinking caffeine containing beverages (69).

Conjunctival reddening is also consistently observed by investigators studying the effect of marihuana and since it is produced consistently by both orally administered marihuana extract and synthetic Delta-9-THC it can be concluded that it is not an artifact caused by irritation from smoke (60,107). The time course of the conjunctival injection, however, does not parallel the effects on pulse rate; the reddening develops slowly, reaches a maximum around 1 hour after smoking, after which it declines (81).

An interesting observation has been reported by Hepler and Frank (56) on the effect of marihuana smoking on the intraocular pressure of 11 volunteer subjects as measured by applanation tonometry. A substantial decrease, averaging about 25% of the initial pressure has been observed in most of the subjects. Further experiments are needed to establish the specificity, time course and eventual consequences of long-term administration of the drug before the implications for possible therapeutic application in the treatment of glaucoma can be entertained.

Among the physiological measurements which are not changed after the administration of marihuana, one may include pupil size (a slight decrease rather than increase can be observed by using sophisticated instruments), body temperature, respiratory rate and deep tendon reflexes (59). Some subtle morphological changes in alveolar macrophages have been observed after smoking marihuana or tobacco, but the phagocytic activity appears to be unchanged (90).

Biochemical Effects

Marihuana smoking or hashish ingestion has long been reported to increase hunger and appetite. Such reports apparently led to the assumption that marihuana lowers blood glucose. In view of the consistent recent findings (67,139) that neither smoked nor orally ingested marihuana has any significant effect on plasma glucose levels, Hollister tested whether or not marihuana stimulates hunger and appetite by measuring food consumption systematically after fasting subjects were treated with marihuana, alcohol, dextroamphetamine, and a placebo (62). Blood samples, drawn before drug administration and just prior to the first offering of food, were analyzed for glucose and free fatty acid content.

While dextroamphetamine and, to a lesser extent alcohol, reduced food consumption and appetite, marihuana had an individually variable stimulating effect on appetite in slightly more than half the subjects. As in previous studies, marihuana had no effect on plasma levels of glucose and free fatty acid.

Podolsky (112) examined the glucose tolerance test in four regular users of marihuana. Although the fasting glucose levels were not significantly different from normals in half of the subjects, significantly higher glucose levels were found 30 and 60 minutes after a standard dose of glucose. The deterioration of the glucose tolerance test in these subjects cannot be explained by abnormal hormone levels involved in the regulation of glucose metabolism since there was no impairment of insulin release or elevation of growth hormone levels.

Neurological Effects

There have been relatively few studies on the neurological effects of marihuana since most of the earlier studies reported only minor changes in the routine tests of neurological functioning (93).

Domino (33) found that marihuana caused a very slight increase in patellar reflex that could be detected only through EMG and strain-gauge recordings of computer averaged data.

Volavka et al (133) studied the EEG in normal volunteers after smoking marihuana. Visual analysis of the paper record detected no consistent drug-related changes. Computerized analysis of the records detected differences among the intercepts of the regression lines for the three drug conditions (placebo, low and high dose of marihuana) which suggests a drug effect of rapid onset. The principal change was an increase in percent alpha time and an associated reduction in theta and beta bands. These results are in agreement with the observation of an increase of power in the 9-10 Hz bands by Rodin et al (115). Surprisingly, there are no reports on the time course of acute marihuana effects on EEG. The fact that EEG records were taken at different times after smoking may partly account for the variety of EEG changes described in the literature as marihuana effects (59,115). Furthermore, no published experiments used a systematic alerting procedure while monitoring EEG. Without alerting, EEG signs of drowsiness may obscure small drug related effects, as indeed Hollister (59) indicates. EEG and behavioral data suggest that marihuana, at dosages typically used, would have just such mild effects (133). Roth et al (116) studied the effect of smoking marihuana and synthetic Delta-9-THC on the auditory evoked response and background EEG in young male chronic users. Components of the auditory evoked response to both frequent and infrequent sound bursts were decreased in amplitude with marihuana, especially in the first few minutes of the stimulation period. There was also initially more alpha power in the EEG with marihuana. Synthetic THC at a dose of 10 mg. showed effects intermediate between placebo and marihuana, although the marihuana cigarettes used contained an equal amount of Delta-9-THC.

Several parameters of spontaneous activity after stimulation measured by Fourier analysis of occipital and vertex leads failed to differentiate the three conditions. The results as measured by the auditory evoked response seem to objectively confirm an increased ability of the subjects to "tune-out" the outside world during marihuana intoxication, which has been reported subjectively by users.

Effects on Mental and Motor Performance

Experiments conducted and published in the past year continued to confirm earlier findings that marihuana and Delta-9-THC consistently affect motor and mental performance in a linearly dose-dependent fashion. The importance of these more recent studies is that the dosage of THC was better controlled than in most of the earlier studies.

Kiplinger et al (81) using a randomized block, double-blind design have found that motor performance, as measured by the error scores on several pursuit motor tasks deteriorated in a dose dependent manner after smoking marihuana. On repeated testings the scores remained relatively constant over the 5 weeks of weekly administration. The mental performance, as measured by nine different verbal tasks on the delayed auditory feedback (DAF) device, deteriorated in only 4 of the tasks used and was unaffected in 5 of them. Significant dose-related changes were found in verbal output, two counting tasks and in a color discrimination task (81).

The same group of investigators have also systematically tested the effect of alcohol separately and together with marihuana in the same tasks (92). At a blood alcohol concentration of 0.05 percent (equivalent to the effect of 3 bottles of beer or 3 ounces of 100 proof whiskey one half hour after consumption) the performance decrements on the above mentioned tasks were about the same as with 2.5 or 5.0 mg. THC (the performance decrements produced by THC in the range studied in this experiment were not dose dependent). When alcohol and THC were consumed together (alcohol first, followed by a marihuana cigarette 30 minutes later) the performance decrements appeared to be additive.

Similar conclusions were drawn by Hollister and Gillespie (63) from their well controlled comparison of orally administered marihuana (calibrated to contain 0.5 mg. of THC/kg. of body weight), Ethanol (1 ml/kg) and dextroamphetamine sulphate (0.2 mg/kg) using a placebo (THC-free marihuana extract) as control treatment. They found that dextroamphetamine tended to improve performance on psychometric tests; the other two drugs tended to impair it. Simple reaction time was significantly impaired by both ethanol and marihuana though the impairment was less pronounced for marihuana (63). Marihuana has been reported to increase complex visual reaction time, and especially to increase variability in performance due to occasional lapses of attention (27). The effect of high doses of marihuana on reaction time has been confirmed by other investigators as well (34,104).

Meyer et al (100,103) have emphasized the significant role previous smoking experience plays in the results obtained in the various laboratory tests with a standardized dose of marihuana. They compared six heavy and six casual smokers in their performance on various perceptual and psychomotor tasks after smoking a fixed dose or an *ad lib* dose with the results in a placebo session. Both heavy and casual smokers showed a modest decrease in perception and psychomotor task performance with both types of marihuana dose, though casual smokers showed a greater degree of impairment than did heavy smokers. The difference in performance on a "Continuous Performance Test" was especially striking: casual smokers making five times as many errors of omission as they did under placebo while no increase in number of errors was found in heavy users. This effect is consistent with Clark's observation that complex reaction time may be impaired, perhaps secondary to lapses in attention (27).

Short-time memory has been singled out by many investigators as the mental faculty most significantly affected by marihuana (1-4,34,97-99,132,133). Abel in a series of experiments tried to determine the way in which marihuana affects human memory (1-4). The analysis of the data indicated that marihuana does not significantly interfere with the retrieval of information already present in the memory. It was shown, however, that marihuana interferes with initial learning, significantly affecting acquisition processes involved in the storage of information (4).

He suggested that an inability to concentrate may be the most likely reason memory is adversely affected by marihuana. In not being able to concentrate, subjects cannot rehearse and, as a result, information cannot be transferred to permanent memory (4,119).

Melges *et al* (97-99) further investigated the relationship of temporal disintegration to the impairment of immediate or short-term memory by marihuana. They have shown that the increased concentration on the present, co-varies significantly with a confusion of past, present, and future and the emergence of a sense of timelessness. The different types of temporal distortions induced by marihuana are, therefore, interrelated processes and may be associated, in general, with euphoric moods (99). The impairment of immediate memory is probably playing an important role in hindering the individual's ability to juxtapose and compare current perceptions with memories and expectations.

Driver Performance

In earlier studies on the effect of marihuana on driver performance controversial results have been published. Crancer *et al* (29) found relatively little impairment on performance in a Simulated Driving test. Others (59,68,91,92) have insisted that because of the significant effect of marihuana smoking on reaction time and other more complex motor tasks, it would be surprising if marihuana, at least at higher doses, did not have deleterious effects on driving performance. Waller (;36) cautions against reaching conclusions from data obtained in a laboratory setting alone and discusses the difficulties inherent in arriving at a definite conclusion on the role of any drug in highway accidents. Manno et al (92) on the basis of their results with marihuana on motor performance in the laboratory, suspects that the negative findings of Crancer et al may have been due to an error regarding THC content of the marihuana used. In a study on the effect of orally administered cannabis and alcohol on simulated driving, Bech et al (9) have found a significant dose-related increase in brake time after ingestion of cannabis.

Other effects of marihuana may also play a role in highway safety. Frank et al (42) reported a marked increase in the amount of time required to recover from glare. This effect was not related to changes in pupil size or illumination threshold, which were negligible, and persisted for several hours after smoking marihuana. This finding may be of significance in view of the unknown number of users who may drive at night while stoned.

Even without being "high" on marihuana there are a few reports that indicate that "flashbacks" may have a relevance to highway safety. Woody (143) published three case reports of young men with histories of hallucinogen usage who experienced visual disturbances while driving. None was "high" at the time of the experience but admitted to a history of multiple drug taking, involving marihuana, hashish, LSD and amphetamines, as well as other types of drugs. These subjects were not involved in any accident at the time of their reported "flashbacks" but they feared that this might happen. Obviously, more research is needed in elucidating the role of various drugs on highway accidents along the lines suggested by Waller (136).

Acute Physical Toxicity

Smith has reported on the acute and chronic toxicity reactions observed in the patient population treated at the Haight-Ashbury Free Medical Clinic (14,22). Common physical reactions reported include nausea, dizziness, and a heavy drugged feeling. These reactions are probably due to an inadvertent excessive dose of marihuana and seem to most frequently occur in inexperienced marihuana smokers or with oral intake.

Death from an overdose of cannabis has been reported extremely infrequently. There are a small number of reports in the older literature of fatal overdose of cannabis (30,36). Heyndrickx et al report the only recent case of fatal intoxication (57). Although they were able to demonstrate the presence of one cannabis constituent in the urine and the patient was found dead in a room containing large amounts of cannabis and smoking paraphernalia, they were unable to find cannabis in the body itself. No other cause of death was apparent but death from overdose of cannabis was not definitely proven.

Gourves et al report a suicide attempt using hashish (49). After recovery, the subject reported consecutively smoking nine to ten large pipefuls of a hashish-tobacco mixture before losing consciousness. This produced coma which lasted for four days. Supportive treatment was given and recovery was uneventful.

Several cases of acute collapse after intravenous use of cannabis preparationshave been reported (55,79,80,89,45). In these cases hypotension, chills and fever, leucocytosis, hepatosplenomegaly, and temporary anuria have been frequently described. All of these patients rapidly developed a severe, acute toxic illness following the injection of the material. The symptoms may have resulted from an acute overdose of one or more cannabis constituents or may have been due to an allergic reaction to foreign substances, to a bacteremia, to the injection of insoluble particles into the bloodstream, or some combination of these factors.

Two case reports describe the use of marihuana associated with the exacerbation of a medical illness. In one report a young man with a history of grand mal epilepsy used marihuana several times over a three week period (74). Although he had ceased taking his anti-convulsant medication six months previously, he had remained seizure free. During the three week period of marihuana use, he had three grand mal seizures. These did not occur during intoxication with the drug nor immediately thereafter. Whether marihuana was related causally to the occurrence of these seizures or was merely temporally associated in a person who had had grand mal convulsions intermittently for many years cannot be ascertained. Other reports have attributed an anti-convulsant effect to marihuana (cf. Therapeutic Use). In another report a case of diabetic ketoacidosis was described in a mental patient after oral consumption of a large amount of marihuana (65). Again, the causal role of marihuana is difficult to assess. Retrospective history-taking revealed no evidence of diabetes prior to marihuana ingestion and there was no family history of diabetes. However, the report does not present laboratory studies done before the ketacidosis or marihuana use which could confirm or rule out the prior existence of diabetes. Experimental administration of THC to humans has not produced evidence of an effect on glucose metabolism (64).

In summary, death from overdose of cannabis is a very rarely reported event. Although the lethal dose for humans is not known, evidence from acute toxicity studies in animals and human case reports of overdose seems to indicate that the ratio of lethal dose to effective dose is quite large and is much more favorable than that of other common psychoactive drugs such as alcohol and barbiturates (111). Intravenous injection may be associated with an acute, severe reaction and seems particularly unwise in view of the insolubility of the drug and the potential for allergic and toxic sequelae inherent in this mode of use. Isolated case reports have associated marihuana with exacerbations of epilepsy and diabetes but a causal role has not been established.

Lundberg et al studied records of over 700,000 consecutive hospital admissions in Los Angeles between 1961 and 1969 and found only nine instances of marihuana-induced admissions (89). A majority of these followed intravenous use of a cannabis preparation and may more properly be considered a complication of the mode of use than results of the drug per se. The authors felt these findings suggested that serious acute effects of smoking or oral ingestion of marihuana are rare.

Chronic Physical Effects

Heavy patterns of cannabis use comparable to those seen in the East have not yet developed in the West. As a result, Western observers have not had the opportunity to observe large numbers of chronic users and to report on possible physical effects of such use. Nevertheless, there are a small number of reports in the Western literature describing chronic effects of Cannabis use.

The relevance to the Western experience of Eastern reports about effects of chronic use is difficult to judge. The many differences in terms of nutrition, disease prevalence, availability of medical care, and public sanitation limit the degree to which one can compare Eastern and Western populations. However, reports in the Eastern literature may serve to alert us to possible chronic effects which might eventually come to our attention in this country if a large chronic-user population develops.

Respiratory difficulties such as bronchitis and asthma have long been reported as complications of heavy Cannabis smoking. Chopra et al and others have reported a high frequency of bronchitis and other respiratory problems in their studies of chronic user populations (21, 22, 66). It should be kept in mind, however, that Eastern smoking mixtures often are a combination of tobacco and Cannabis. In the West, Mann et al studied the effect of marihuana smoking on alveolar lining material and pulmonary macrophages (90). Using the electron microscope they were unable to distinguish any differences between tissue of marihuana smokers and non-smokers. This was in contradistinction to tobacco smokers who showed easily recognizable changes. The level of usage of these marihuana smokers probably could be characterized as moderate rather than heavy. Tennant et al have recently reported on a population of soldiers in West Germany who used hashish very heavily (130). A majority of these patients had respiratory complaints which included bronchitis, sinusitis, asthma, and inflammation of the nose and throat. In five of the patients who showed evidence of bronchitis, pulmonary function studies were performed which showed evidence of a mild obstructive condition. This seemed to improve with diminished smoking of hashish. Less frequent complaints of these patients included recurrent urticaria, acne, abdominal cramps, and diarrhea.

Kew et al have reported studies of twelve frequent marihuana users who were said not to use intravenous drugs or alcohol. Eight subjects were found to have evidence of mild liver dysfunction (78). Some changes were observed in three of the subjects in liver biopsy material. The authors concluded that their findings were not unequivocal and might be due to factors other than marihuana, but they felt that their findings indicated the need for further detailed study of liver function in marihuana users. More recently Hochman and Brill have studied fifty frequent marihuana users, all of whom denied significant alcohol use prior to the study (58). A number of laboratory tests of liver function were done, and ten of these subjects showed indications of disturbed liver function. After confrontation by the investigators each subject admitted to long-term use of alcohol before use of marihuana. All disclosed that they had continued regular use of alcohol at heavy levels of consumption and several admitted to episodes of binge drinking. The subjects were asked to abstain from alcohol for one month while continuing their usual pattern of marihuana use. All except one had a disappearance of evidence of disturbed liver function. Although this study does not unequivocally prove that marihuana does not affect liver function, it does vividly illustrate a fact well-known in clinical medicine for some time. That is the difficulty of getting accurate and reliable drug and alcohol histories from patients who abuse these substances. In their study of 31 heavy hashish users Tennant _et al_ found no evidence of liver dysfunction (130).

Reports from the East have described an obliterative arteritis of the lower extremities seen in young Moroccan males who are heavy cannabis users (125). The progress of the disease was felt to closely parallel cannabis intoxication. Epidemiologic studies have not been reported which would indicate the incidence of arteritis in a comparable population of non-users. Halpern and Citron have reported evidence of a necrotizing arteritis seen in drug abusers in this country (53). However, these subjects were multiple drug users and the most common factor among them seemed to be a history of intravenous use of methedrine.

Kolansky and Moore in a report on adolescent marihuana users seen in their psychiatric practice felt that there were gross indications of neurologic impairment in a few heavy user patients (83). They reported observing such things as slurred speech, staggering gait, hand tremors, and disturbances in depth perception. They did not, however, actually perform neurological examinations on these patients, therefore such findings are difficult to assess.

A very recent article by British investigators has reported the existence of cerebral atrophy in young cannabis smokers (18). Evidence of cerebral atrophy was obtained by air encephalography in 10 male patients with histories of consistent cannabis smoking over a period of

3-11 years. All of the patients were multiple drug users with LSD and amphetamines being the most commonly used drugs after cannabis. The patients were selected because of their history of cannabis use and because they presented a variety of behavioral and neurological symptoms. A group of 13 patients in the same age range who had normal encephalograms were used as a comparison group. Ventricular dilatation consistent with cerebral atrophy was felt to be present in the drug-using patients. The authors concluded that their findings suggest that regular use of cannabis produces cerebral atrophy in young adults and emphasize the need for future studies of the neurological consequences of drug abuse.

Although the authors feel they have demonstrated cerebral atrophy in association with heavy cannabis use, others have questioned if cerebral atrophy can be accurately demonstrated with this radiographic technique (144). Even if atrophy is present, it is not proven that such changes were caused by cannabis. Other drugs were used by all of the patients and could have played a role in the pathological changes found. Some reports have implicated amphetamines in organic brain damage and 8 out of 10 of these patients admitted to amphetamine use although the authors felt that other drug abuse was not sufficient to have caused the changes observed. The reliability of the patients self-reported drug abuse histories is unknown but the difficulties of obtaining reliable histories from drug users has been alluded to earlier in this section. In addition, it must be noted that the patients were selected because of neurological and behavioral symptoms while the comparison group were selected because they had normal air encephalograms. Nevertheless, cerebral atrophy is a finding of such seriousness that the report requires careful consideration and emphasizes the need for further study in this area.

A number of minor physical effects associated with the use of cannabis have been reported by Eastern and Western writers. Such things as weight loss, gastrointestinal complaints, congestion of the ciliary vessels of the eye, and sleep disturbance have been reported (20,21,123). A few of the patients in Tennant's study reported abdominal cramps and diarrhea but these complaints are not commonly associated with cannabis use in the Western literature. Tennant also reported evidence of an allergic phenomenon with three of his patients reporting recurrent urticaria associated with hashish use.

Recently a single case report has appeared which describes an anaphylactoid response in a twenty-nine year old housewife after smoking a marihuana cigarette for the first time (88). Skin tests gave positive evidence of allergy to marihuana constituents. The authors felt that in view of the large number of people reported to have used marihuana and the paucity of reports of allergic reactions that the allergenic potential of marihuana may be quite low. It was noted, however, that other factors might prevent reporting of similar cases and if this were the case then marihuana allergy might be more common than is generally supposed.

In summary, both Eastern and Western literature contain little evidence at this time that light to moderate use of cannabis has deleterious physical effects. (An occasional allergic reaction may be an exception to this, but these seem to be very rare.) Almost all reports of physical harm from cannabis use are based on observations of moderate to heavy, chronic use of the drug. Eastern reports have frequently mentioned bronchitis and respiratory problems associated with heavy chronic use and

Tennant's case studies would seem to support these observations. Although some authors have reported evidence of mild liver dysfunction in marihuana users, others have been unable to confirm these findings. Arteritis has been reported to be assiciated with marihuana use in Morocco, but this finding has not been reported in other areas of chronic use and no conclusion can be reached about it. Some have reported evidence of neurological dysfunction but a causal role of cannabis has not been definitely established and they await confirmation or refutation by other investigators. Finally, the difficulty of proving a causal relationship between chronic use of any drug and a resulting illness should be kept in mind. Observation for many years is often necessary with heavy reliance on epidemiologic and statistical methods. The recent example of the role of cigarette smoking in certain illnesses illustrates many of the problems involved. For these reasons it is likely to take many years of study before the full story on possible physical effects from chronic use of marihuana will be complete.

Careful studies of foreign populations of chronic cannabis users are now under way in an effort to provide more information about chronic effects without having to wait many years before our own chronic users become appropriate subjects for study.

Preliminary results from an intensive medical, neurological, and psychiatric study of 31 male chronic hashish users in Greece have shown few abnormal findings (39). Although it is too early to draw conclusions from this study, some findings are of particular interest in view of the reported association of cerebral atrophy and cannabis abuse. These subjects ranged in age from 26 to 69 years with a mean of 46.1 years. Age at starting the use of hashish ranged from 13 to 35 years with a mean of 18.7 years. Average years of use was 27.6. Eight of the subjects reported use of alcohol and one subject reported that he had used opiates. Other drug use was denied. In this group there was an absence of significant neurological signs and symptoms and it was reported that none showed evidence of an organic brain syndrome. An EEG was recorded on all but one of the individuals and independently reviewed by four different encephalographers. Twenty-five of the EEG records are felt to be within normal limits. One record is felt to require further evaluation but probably does not indicate significant pathology. An abnormal record was found in a subject who had had a recent head injury. Three other records were felt to be characteristic of cerebral dysfunction. The significance of these findings can not be fully judged until data from a comparable control group has been analyzed.

In another foreign study conducted in Jamaica, matched non-users control and chronic cannabis user groups were studied. Each group consisted of 30 individuals. Ninety per cent of the users were daily smokers of cannabis and the remaining experimental subjects had used the drug a minimum of several times a week for many years. Extensive medical, neurological, psychological, and psychiatric investigation has shown little evidence of significant differences between the two groups. Again it must be emphasized that these are preliminary findings and await more complete analysis before conclusions can be reached (117).

Genetics and Birth Defects

Because of the reported widespread use of marihuana, particularly by those in the reproductive age group, there has been concern about possible genetic effects or birth defects caused by cannabis. However, at the present time, there are only a few preliminary studies reported in the literature.

In an animal study using the rat, Martin found no difference in the frequency of chromosome abnormalities between controls and those exposed to cannabis preparations (94). Neu et al examined the effects of Delta-8- and Delta-9-THC added to human leucocyte cultures (105) and found no evidence of structural chromosome damage though there was a decrease in the rate of cellular division. Dorrance et al examined human lymphocyte chromosome abnormalities in a group of marihuana-only users, a group of LSD users, and a group of age-matched controls (35). No statistically significant differences were observed among the three groups. Gilmour et al examined peripheral blood leukocytes for chromosomal aberrations in a group of 56 users of psychoactive drugs and compared them with a group of 16 non-user controls (48). No significant differences were noted between the controls and a marihuana-only group although it should be stressed that the marihuana group were only light users.

Three human case reports have reported cannabis use associated with birth defects in offspring, though in all of these instances other drugs including LSD were also used (54,19,46).

Because many marihuana users are also multiple drug users, it is often difficult to attribute any observed abnormality to marihuana. Some authors have suggested that in multiple drug users some common factor other than the drug may be responsible for increased frequency of chromosome aberrations observed (48). Thus far, in a small number of preliminary studies, there has been no evidence that cannabis causes chromosomal aberrations. The number of clinical reports of birth defects in children of mothers who use cannabis has been very small especially considering the large number who are believed to have been exposed to the drug. A number of studies are underway which investigate this problem in more detail. In the meantime, the use of any drug of unknown teratogenic or mutagenic potential is unwise especially by women during the reproductive years.

Cannabis and Psychiatric Illness

In this section we will deal with the role of cannabis in a variety of psychological states ranging from "adverse reactions" to chronic psychoses and the so-called amotivational syndrome.

To better understand the many reports of the psychological effects of marihuana, it may be useful to briefly reiterate those factors which are important in determining the effect of any psychoactive drug. The behavior that results from taking such a compound is determined by variables which can be grouped into three broad categories. The first category concerns the pharmacological properties of the drug and the dose received. The second has to do with the psychological state of the individual at the time the drug was taken and includes such things as personality structure, attitudes about drug taking, expectations, etc., (i.e. his "set"). The third category has to do with the setting in which the drug was taken. Experiments with hallucinogenic drugs have shown the importance of these factors in determining drug effect [37,] (126) and a number of authors describing patients with adverse psychological reactions to marihuana have emphasized the importance of psychological state and the setting of use in producing the distress [140] (13,121).More recently experimental work has demonstrated the role of these factors in the subjective effects produced by marihuana (71). It seems clear that effects which are considered adverse by some subjects may be actively sought by others. Bialos (13) has emphasized that the term "adverse reaction" is a complex one that entails a value judgment. Thus, any attempt to assess the health consequences of psychoactive drug use should keep in mind the role of non-drug factors in producing adverse psychological reactions.

Many of the reports of a connection between marihuana and mental illness come from India, Africa and the Middle Eastern countries. Most of these countries are economically and scientifically underdeveloped, and the standard of medical care is well below that in the West. In addition, those who are mentally ill are often given the lowest priority in the medical care system because there are so many other pressing health problems. Well-equipped mental hospitals and well-trained psychiatrists are uncommon. Therefore, in evaluating studies on marihuana and psychosis which come from these health care systems, it is important to keep in mind the amount of time and effort which is likely to have been given to the careful diagnosis and evaluation of patients. In addition, many chronic illnesses which in themselves may affect mental function still persist in these countries. Finally, most of these studies suffer from such methodological defects as lack of control for many variables, biased sampling, and poor data collection techniques.

One of the earliest examinations of the relationship of cannabis to psychosis was that of the Indian Hemp Drugs Commission (66). It was popularly believed in India that marihuana could produce insanity and many mental institutions reported a high frequency of cannabis psychosis. Upon investigation the Commission found that impressions by non-physicians, such as magistrates and policemen, often were used to make the diagnosis of cannabis psychosis. In order to form its own conclusion, the Commission examined all admissions to Indian mental hospitals in the year 1892 and came to the conclusion that cannabis consumption was a factor in no more than 7-13% of the cases.

Since that time a number of reports on the Indian experience with cannabis psychosis have been published (24,25,32, 106) with varying estimates of the importance of cannabis psychosis. Several reports have described the Moroccan experience (10,26,31). One of them reported that 68% of all mental hospital admissions were cannabis users and that 25% of these admissions were due to cannabis psychoses (10). Reports on cannabis use in South African mental patients have indicated that 2 to 3% of admissions were due to the use of dagga (138). In West Africa one author reports that 14% of psychiatric patient admissions in Nigeria used cannabis (14). Half of these were considered to have toxic psychoses due to cannabis while the other half were felt to be aggravations of a schizophrenic illness.

Good data from these countries on the prevalence and incidence of psychosis in cannabis users and in non-users is not available. This fact, plus the difficulty in distinguishing between a cannabis psychosis and other psychoses such as schizophrenia, makes it very difficult to assess the role of cannabis use in mental illness in these countries.

The problem of elucidating a cannabis psychosis is made particularly difficult by the fact that there are no symptoms which can be specifically attributed to it and not to other psychiatric syndromes. Several Eastern authors have described the clinical characteristics of the cases observed by them (10,23,24,32). The diagnosis of cannabis psychosis usually rests more on the history of heavy marihuana or hashish use than it does on any other factor. Other characteristics such as its self-limited nature and failure to progress to a full schizophrenic picture have been described but are more difficult to evaluate. In spite of these problems, there do seem to be some similarities among the cases reported by different observers in the East. Generally, most authors describe what is felt to be an acute toxic state usually occurring after heavy use. It is characterized by acute or sub-acute onset, confusion, visual and auditory hallucinations, paranoid ideation, excitation or aggression, and amnesia for the period of onset. This syndrome is usually self-limited and lasts from a few days to a few weeks. Some authors have emphasized the manic nature of the syndrome (32). A more chronic version of this same picture is described, sometimes with an acute onset and sometimes with a more gradual onset. Finally, a chronic recurring psychosis with character deterioration and possibly organic brain damage is described, but the distinction between this and chronic schizophrenia is exceedingly unclear. The most frequent picture described in the Eastern reports seems to be the acute toxic state (23).

In the West, the widespread use of cannabis is of more recent origin as are most reports of its role in causing psychiatric problems. It must be kept in mind that there are substantial differences in the amount and duration of usage of marihuana between typical Eastern and Western users. However, there are some earlier reports in the Western literature about marihuana-induced psychosis. Bromberg in 1939 reported 14 cases of what appeared to be an acute toxic psychosis after use of marihuana (17).

All symptoms cleared rapidly within a few days. Because of concern about American soldiers using cannabis in the Panama Canal Zone, some early studies were performed there. In 1933 Siler reported on 34 soldiers who were marihuana users (120). They were hospitalized and studied while being allowed to smoke marihuana as they wished. Although some soldiers smoked several cigarettes per day, few adverse effects were noted. It was observed that they showed no tendency to aggressiveness nor any evidence of psychosis. As part of the LaGuardia report of 1944, Allentuck and Bowman reported "psychotic episodes" in 9 out of 77 subjects during experimental administration of marihuana to prisoners (6,7). Most of these cleared rapidly although 3 had prolonged symptoms. Interest in cannabis and psychiatric illness then waned and remained dormant until an upsurge of reports began in the late 1960's parallel to the reported marked increase in usage in this country.

In considering the more recent reports of adverse psychological consequences of marihuana use, it is well to keep in mind the difficulties inherent in the term as was discussed earlier. In addition, the problem of assessing marihuana's relationship to psychosis is complicated by the fact that some authors of case reports do not carefully distinguish between what seem to be panic reactions or transient paranoid ideation and a full-blown psychosis. This adds to the difficulty in comparing reports in the Eastern and Western literature.

Smith has reported the experience with adverse marihuana reactions in the Haight-Ashbury Free Medical Clinic (121, 122) He has emphasized the importance of personality factors, user inexperience, and an oral route of administration as factors predisposing to a toxic reaction. A number of other reports of adverse reactions have appeared in the literature (13,51 73,140). They embrace a wide variety of distressing subjective effects which include such things as panic, fear, depersonalization, confusion, disorientation, depression, and paranoid ideation. Some authors have reported seeing a number of patients complaining of "flashbacks" of psychotomimetic experiences following marihuana use (13,38, 75,102). Apparently some users have reported that their marihuana highs changed after they began using hallucinogens. How frequently "adverse reactions" may occur in users and not be considered distressing is unknown. However, some studies suggest that that they may not be infrequent. Keeler interviewed 56 marihuana users, 6 of whom reported that they experienced hallucinations of color, design, or had marked perceptual changes (76). Some reported that they could routinely cause this by smoking large amounts. In one study which compared 12 heavy with 12 casual users (103), all subjects reported that at times they experienced such things as thought disruption, depersonalization, recent memory impairment, and paranoid thoughts. With the availability of standardized doses of the psychoactive principle, Delta-9-THC, a number of studies have been done with the experimental administration of marihuana. Some of these have reported the presence of auditory and visual hallucinations in some subjects at high dosages (59, 67), thus suggesting that marihuana may resemble the psychotomimetic drugs under some circumstances. The experimental administration of marihuana under controlled conditions has been associated with an acute psychosis in at least one subject. However, there was evidence of a pre-existing emotional disturbance in this case (41).

Many authors from the United States and scattered reports from Britain, Scandinavia, and the West Indies have described a variety of psychotic states associated with cannabis use. Some of these reports (13,102, 110,140) describe a state characterized by panic and a fear of dying with some paranoid ideation which clears very rapidly and responds to support. This may more properly be considered a panic reaction than a psychosis. Kaplan reports 5 cases of psychotic reactions after smoking marihuana (72). Some seem to fit the picture of a toxic psychosis with rapid recovery, but others recovered very slowly and required extensive treatment. Although the author feels that this "marihuana syndrome" is different from schizophrenia, the reported high incidence of schizophrenia and borderline states in these patients and their families may argue against this interpretation. Others have reported transient episodes of a toxic-type psychosis after use of marihuana (8,50). In Britain, George reports a case with two widely separated psychotic episodes occurring after marihuana use in a patient who was also under considerable marital and financial stress (47). Initially the picture was one of confusion, disorientation, and memory loss, but this was followed by a more chronic picture with thought disorder, hallucinations, and incongruous affect. This picture eventually responded to treatment. In a report from Scandinavia, 7 cases of psychosis in connection with cannabis use were described (11). Four were acute episodes in what were felt to be intact personalities while 3 seemed to be aggravations of schizophrenic conditions. Acutely all showed hallucinations, anxiety, paranoia, and outbursts of agitation. Spencer reports 12 cases of psychosis in marihuana users in the West Indies (124). These showed sudden onset, amnesia, and other manifestations of psychosis. Particularly prominent was a manic component with psychomotor overactivity and flight of ideas.

Some reports from the United States have emphasized the chronic nature of the disturbance felt to be caused by marihuana use. Perna reports a case of psychosis which had an extended course requiring treatment with anti-psychotic drugs, ECT, and psychotherapy (108). Since this patient reportedly had required psychiatric treatment prior to the use of marihuana, it is difficult to evaluate the exact role of marihuana in his difficulties, although it may have precipitated more serious psychopathology. In a widely publicized report, Kolansky and Moore described behavior problems, suicide attempts, sexual promiscuity and psychoses in 38 adolescent psychiatric patients who used marihuana (83). They attributed all of these problems to marihuana use and on the basis of retrospective information felt that there was no evidence of prior psychopathology. This study illustrates the difficulty in interpretation of attempts to establish a causal role for marihuana using retrospective analysis, biased sampling, and ignoring the prevalence of psychopathology in a comparable population. Keup reports 14 cases of psychotic symptoms associated with marihuana use which were admitted to Brooklyn State Hospital in a twelve-month period (77). These cases were quite varied but generally there was evidence of a high level of pre-existing psychopathology in many of them.

Because of the reports of widespread cannabis use among soldiers in Vietnam, the reports of adverse reactions from there are of particular interest. Talbott and Teague reported 12 cases of what appeared to be an acute toxic psychosis following use of marihuana for the first time (127). Most of these cases cleared in 1 to 4 days with no sequelae. They also reported seeing many less serious reactions such as anxiety states, depression, dissociation, depersonalization, disorientation, paranoid thoughts, and hallucinations. In another report from Vietnam it was reported that about 5 cases per month out of a population of 45,000 troops presented with a psychosis associated with a history of marihuana use (28). Again there appeared to be an acute onset after heavy marihuana use with some organic features to the psychosis. The authors felt that the presence of a personality disorder or a borderline personality state were predisposing factors in the development of a cannabis psychosis. Bey and Zecchinelli report on 20 cases of soldiers with acute psychotic reactions associated with marihuana use (12). Acute symptoms consisted of hyperalertness, irritability, suspicion, fearfulness, ideas of reference, persecutory delusions, disorientation and confusion. All cases recovered rapidly with treatment. In studying the personality characteristics of these patients, the authors emphasized that all appeared to be coping with core problems of identity diffusion, ego weakness, low self-esteem, and an inability to form close interpersonal relationships. Most were felt to represent borderline personality disorders.

A number of articles have attempted to estimate the incidence of psychotic and other adverse reactions to marihuana. Keup reported that in a twelve-month period at Brooklyn State Hospital 0.9 per thousand of admissions were directly attributable to cannabis use while in 1.9 per thousand it was a contributory factor (77). Bialos reported 11 cases seen in the Yale Student Health Clinic out of a student population of 8,500 in the academic year 1968-69 (13). Lundberg et al have reviewed the admissions to Los Angeles County Hospital between 1961 and 1969 (89). Marihuana was found to be listed as the cause for admission in only 9 of 700,000 admissions. The majority of these were the result of intravenous administration. This was in sharp contrast to the large number of admissions due to alcohol, barbiturates, and other non-medical use of drugs. Although these figures would suggest that serious adverse reactions to marihuana are relatively infrequent, a more definitive answer awaits further epidemiological study.

In an attempt to elucidate the problem of the causal role of marihuana in psychiatric problems, Halikas et al compared one hundred regular users with fifty of their non-user or casual user friends (52). Each subject underwent an intensive psychiatric interview and history-taking. It was found that half of each group fulfilled the criteria for some psychiatric diagnosis. Most of the diagnosed psychiatric illnesses began before first marihuana use. Anti-social behavior more often preceded marihuana use than followed it. The authors concluded that the high incidence of psychopathology among the controls indicated that at least some regular marihuana users come from a population predisposed to psychiatric illness.

To summarize, it seems clear that marihuana use can precipitate certain less serious adverse reactions, such as simple depressive and panic reactions, particularly in inexperienced users. However, non-drug factors may be the most important determinants in these cases. In addition, there is some reason to believe that it may precipitate psychotic episodes in persons with a pre-existing borderline personality or psychotic disorder. There is considerable similarity in clinical description between the "acute toxic psychoses" reported in the Eastern literature and the acute psychoses described in a number of Western reports. All seem to occur primarily after heavy usage which is greater than that to which the individual is accustomed. These psychoses have some characteristics of an acute brain syndrome. They seem to be self-limited and short-lived if the drug is removed. Some reports have described a more prolonged psychotic course after such an initial acute phase, but the possibility of other psychopathology in these cases has not been ruled out.

The reports from Vietnam which emphasize the stressful conditions and possible pre-existing personality disorders of many of these patients suggest that even in the acute psychoses non-drug factors may be quite important. The fact that in some studies of experimental administration of marihuana, some of the subjects reported hallucinations at high doses, suggests that marihuana may act as a psychotomimetic under some conditions. It is possible that euphoria, hallucinosis, and acute toxic psychosis may turn out to be different points along a dose-response continuum for the drug, although further experimental investigation is required in this area before any conclusion can be reached. At the present time evidence that marihuana is a sufficient or contributory cause of chronic psychosis is weak and rests primarily on temporal association. Further epidemiological and controlled clinical studies are necessary in order to clarify this important issue.

It has been suggested that regular use of marihuana may produce subtle personality changes called the "amotivational syndrome" (16,83,141). The central features seem to be a loss of conventional motivation and a preoccupation with drug-taking and its subculture. Some have suggested that marihuana causes organic brain changes which produce this syndrome, though there is little objective evidence at present to support this view (141). A similar syndrome is described in the Eastern literature (10) though there it appears to be associated with much heavier use of cannabis than is usual in the West and may be a chronically intoxicated state comparable to that of the skid row alcoholic in this country. Obviously, individuals in a state of chronic intoxication are unlikely to show conventional levels of motivation and the time required to obtain and consume enough material to maintain such a state is not likely to leave much time for other pursuits. Therefore, the relevant question would seem to be whether or not the regular use of marihuana at a level below chronic intoxication may bring about personality changes through mechanisms other than the immediate pharmacological effects of the drug. Scher describes his experience with patients who are regular marihuana users (118). Although most of these patients were functioning members of society, they began to experience a vague sense that something was wrong and that they were functioning at a reduced level of efficiency. The fact that depressive syndromes can produce a similar picture illustrates the difficulty of interpreting such reports. Sociological factors add to the problems of interpretation since much drug use is associated with a youth counterculture which often rejects the more conventional orientation. The fact that heavy marihuana users may have a high incidence of pre-existing psychopathology raises the question of whether or not any decreased interest and motivation observed in them may be a function of the psychopathological condition rather than of the drug. Therefore, the question of whether or not there exists a causal relationship between cannabis and an amotivational syndrome or only an associative relationship remains to be answered.

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IX. THERAPEUTIC USES OF CANNABIS

Therapeutic Uses of Cannabis

Use of cannabis preparations or derivatives is not a medically accepted treatment for any illness in the United States today. However, cannabis has long been used and continues to be used as an indigenous medicine in the South of Africa, in some parts of South and Central America, Turkey, Egypt, and many areas of Asia, including India, the Malays, Burma and Siam.

The Indian Hemp Commission Report of 1893 called Cannabis indica one of the most important drugs of Indian Materia Medica considering the effects of hemp drugs, believed it expedient to take up first their medicinal use and pointed out that this use means not only use prescribed by physicians but also use as folk medicines. The Commission heard testimony from a total of 1,193 Indian and European witnesses, and almost two thirds of them referred to the use of hemp drugs by the Vedanti and Yunani schools of native physicians. About one third of these witnesses referred specifically to the use of ganja, one third to bhang, and the remainder stated that both forms of the drug were prescribed. Several witnesses from the Northwestern Provinces and the Punjab characterized charas as a remedial agent.

The Commission also took into account the duration of use of cannabis as a medicine, and stated that the use of bhang between the fifth and twelfth centuries is frequently mentioned in dictionaries.

For example, in the Makhzan-el-Adwiya, the qualities of the hemp plant are said to be both stimulant and sedative.

> "The leaves of the plant made a good snuff for deterging the brain; the juice of the leaves applied to the head as a wash remove dandruff and vermin; drops of the juice thrown into the ear allay pain and destroy worms and insects. It checks diarrhea, is useful in gonorrhea, restrains the seminal secretions, and is diuretic. The bark has a similar effect. The powder is recommended as an external application to fresh wounds and sores and for causing granulations; a poultice of the boiled roots and leaves for imflammations and erysipelas and for allaying neuralgic pains."

Rumphius in the Herbarium Amboinense 1695, stated that the Mohammedans in his neighborhood frequently sought marihuana from his garden for those afflicted with virulent gonorrhea or asthma. He also added that the powdered leaves check diarrhea and that hemp smoke can be used as an enema in the treatment of strangulated hernia.

The Indian Hemp Commission reported that the preparations of the hemp plant used by native doctors were bhang, ganja and sometimes charas; the seeds appear to have been very rarely used. Bhang was generally prescribed as a cold infusion prepared from powdered leaves,as a local application in the form of a poultice. When ganja and charas were prescribed for inhalation, the drugs were smoked mixed with tobacco; when ganja was used for local fumigation the smoke from the unmixed drug was employed. The two drugs appear to have rarely been used for internal administration.

Witnesses who appeared before the Indian Hemp Commission reported that the drug was used extensively in treating diseases of the nervous system - including headache, brain fever, neuralgia, sciatica, convulsions in children. One of the commonest uses was for the relief of protracted labor pains, dysmennorhea, toothache, and as a local anaesthetic in extracting teeth.

From a public health standpoint, probably one of the most interesting uses of hemp was for the treatment of cholera during epidemics. In addition, the Commission found that use of the drugs was recommended in malarial areas to counteract the effects of "bad air and water." The report states "in both these cases hemp drugs probably act as indirect prophylactics, stimulating the nervous system and allaying depression, thus serving the same purpose as the popular use of alcoholic beverages by the lower classes in Europe during the prevalence of epidemics."

It might be remembered that even in the United States, after World War I, alcohol was prescribed to ward off influenza during the epidemic of that disease.

In Europe and America, interest in the medical applications of cannabis was stimulated by the work (1838) of Dr. W. B. O'Shaughnessy, a thirty year old assistant surgeon and professor of chemistry in the Medical College of Calcutta. He performed some simple observational animal experiments to determine whether or not the drug was safe, and then began to experiment with it in patients suffering from such diverse ailments as rabies, rheumatism, epilepsy and tetanus. He found tincture of hemp to be an effective analgesic and to have anti-convulsant and muscle-relaxant properties (11).

During the period from 1840 to 1900, more than 100 articles were published in Western medical journals recommending its use for various somatic and psychic complaints. However, physicians were not uncritical, nor did they see cannabis as a universal panacea, they knew that some preparations become inactive because of aging or of improper storage conditions, and recognized the importance of gradually arriving at the appropriate dose for an individual so as to avoid toxic effects. For example, Dr. J. R. Reynolds summarized 30 years of experience in dealing with cannabis by pointing out that he had found it most helpful in the treatment of certain neuralgias, including tic douloreux (15). He had also found it useful in the treatment of migraine, stating that many of his patients had been able to ward off the worst effects of the malady by taking hemp at the onset of the attack. He states that it had been of help in treating certain epileptoid states, depression and dysmennorrhea. He also listed a number of ailments for which he had found the drug to be relatively ineffective.

It was during the mid-nineteenth century that cannabis was first seriously proposed in Western medical literature as an agent useful in the treatment of psychiatric illness. J. J. Moreau de Tours in 1845 wrote of its use in the treatment of melancholia (particularly with idée fixe), hypomania, and chronic mental illness in general (3). There were many articles in the succeeding decades which either supported or disputed its utility in the treatment of various mental illnesses.

In the United States, cannabis, even before the passage of the 1937 Marihuana Stamp Act, began to fall from favor as a drug of choice in the treatment of physical and mental disorders for various reasons. These included the variable potency of different batches of the drug, the variability in reactions of persons to the drug, its lack of water solubility so that it could not be easily injected, and its delay in acting after ingestion. In addition, other drugs such as morphine and the barbiturates were coming into increasing use. It should be mentioned, however, that the decline in the use of cannabis was apparently not connected either with its intoxicating properties or with its addiction liability.

The relevance of these early reports of cannabis use to modern medical practice is difficult to evaluate. Most were clinical case reports lacking controls or other standardized conditions of experimental design which we have come to expect in the modern evaluation of a therapeutic drug. In addition, there was the problem of not knowing what the active principle was nor how much was present in the preparation. Some of these difficulties were partially overcome when, around 1940, a semi-synthetic analog of tetrahydrocannabinol was developed (1). This allowed better dose standardization than had previously been possible, and there followed a number of studies investigating the therapeutic usefulness of this new compound, "synhexyl."

Both favorable and unfavorable reports were made about the benefit of the drug in depression (12,13,18,19). Some investigators felt that it was useful in treating the alcohol abstinence syndrome (19). There is at least one case report of successful use of marihuana as a replacement for alcohol (10). After animal experiments indicated an anticonvulsant activity which seemed to be similar to that of diphenylhydantoin (7), clinical tests were done with mentally retarded children who suffered from severe epilepsy that was poorly controlled by other drugs (2). Most of these children seemed to do as well on "synhexyl" as on their previous drug and some seemed to do much better.

After this upsurge of interest, little further was done to investigate the therapeutic application of cannabis until the very recent interest in the drug as a result of its widespread use in our society. One exception to this was the demonstration that effective antibacterial substances existed in cannabis preparations (4,6,14). Since the antibacterial properties seemed to be inactivated by blood and serum, and because of poor solubility, cannabis preparations did not seem suitable for parenteral use. However, clinical trials with topical preparations were carried out (6). Favorable results were reported in the treatment of acute and chronic otitis, sinusitis, and a variety of dermatological conditions.

At the present time the therapeutic role, if any, of cannabis preparations remains unclear. Although its use has been reported in a large number of conditions, there is an almost total absence of therapeutic efficacy studies which meet the criteria of modern scientific methodology. The older reports suffer from numerous deficiencies and, in addition, other drugs which possess proven therapeutic effectiveness have now been found for use in many of the conditions which formerly were treated with cannabis. The more recent studies of the successful use of cannabis derivatives in the treatment of depression, alcoholism, seizures and infections lack controls and can only be considered as preliminary case reports which await further confirmation.

The discovery by Mechoulam in 1965 of Delta-9-THC, the major psychoactive principle in marihuana (9), has paved the way for the development of preparations of known dose and potency which are now available for investigational uses. This, along with preclinical toxicity studies may make it possible in the near future to do well-controlled therapeutic efficacy studies. Renewed interest has also developed in the psychotherapeutic potential of marihuana and its constituents. Suggestions have been made that it may be useful in relieving suffering and producing euphoria in patients suffering from chronic diseases (16). Marihuana's consistent cardiovascular effects have caused speculation that it may prove useful in hypertension (17). Very recently it was reported that use of marihuana decreases intraocular pressure, thus suggesting the interesting possibility that the drug may be useful in treating eye diseases such as glaucoma (5).

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X. FUTURE RESEARCH DIRECTIONS

FUTURE RESEARCH DIRECTIONS

Substantial gains in our knowledge of many aspects of marihuana have been made during the past year. As we have outlined in previous sections much has been learned about the nature of cannabis, its chemistry, toxicology, acute effects and metabolism. While much remains to be learned, systematic exploration of the implications of chronic use in man has also begun. The changing psychosocial characteristics of users are being more clearly defined and we have a much better idea of the nature and extent of use in the United States. As our knowledge has expanded so has our awareness of the complexity of the problem.

The purpose of this section is to give an indication of the continuing and expanded research activities planned or underway in the Department mainly through the National Institute of Mental Health, the agency with primary responsibility for the marihuana research program.

Although there is now an assured supply of natural and synthetic material, there is a need to develop supplies of new compounds such as marihuana metabolites which have become important to research. A continuing effort is also being made to better understand the properties of the material. While an understanding of the botany of the plant may seem remote from its health implications, it is useful in better comprehending the differences in potency of material available both here and abroad.

Attempts are currently underway to develop a way of systematically monitoring street drugs. Such an effort would enable us to learn more about the characteristics of marihuana and hashish available to the illicit user and about its possible adulterants. Such information would be very useful in enabling us to more closely duplicate street use conditions in the laboratory. It would also be a valuable asset in educating potential users to unusually hazardous drugs and in dissipating some of the mythology which surrounds the drug seller's enterprise.

As a result of the research on metabolic aspects we have become aware of some of the metabolic transformations the drug undergoes. In order to gain insight into the mode of action we are attempting to synthesize some of the principle metabolites so that they too may be studied in detail. At the same time a continuing attempt is being made to determine the biological activity of the many other cannabis constituents which may have either toxic implications or affect the psychoactive properties of what is currently believed to be the principal psychoactive ingredient, delta-9-tetrahydrocannabinol (THC).

Human "balance" studies are planned in which the intake and excretion of marihuana constituents and their metabolites are determined. This is in order to study the possible accumulation of delta-9-THC or its metabolites. An animal model of human THC metabolism in which the mode of biotransformations is qualitatively and quantitatively similar to man is also being sought so as to more adequately study the metabolism of the drug.

Basic work on the metabolism of the drug and particularly its effects on the biochemistry of the brain is being presently supported and expanded research is being actively encouraged. While metabolite concentrations have been correlated with brain area concentrations by radioactive methods, much needs to be learned about the specific mode of action of cannabis.

Work is continuing on the development of a practical means of measuring the amount of cannabis which becomes biologically active in the body in a manner somewhat analogous to blood alcohol determinations for examining the level of alcohol intoxication.

Administration of the natural and synthetic material to volunteer subjects for periods of up to one month is ongoing and should considerably enhance our understanding of the implications of longer term use under well controlled conditions.

Because the action of marihuana on the cardiovascular system is one of the most reliable indicators of its activity, the mechanism of action and its possible toxic significance are being investigated. Its characteristic acceleration of heart action may entail risks to those with heart disease. As use expands to include older populations, assessment of the risks posed for those with less adequate cardiovascular functioning may be of considerable importance.

Since smoking is the predominant mode of ingestion of marihuana and reports of respiratory complaints have been associated with chronic use, investigation of the effects on lung function are also of basic importance. Several studies currently underway are concerned with this question. While the carcinogenic potential of marihuana appears to be low because of the relative small amounts typically inhaled, more detailed studies are underway or planned. In one study an animal model utilizing beagles has been developed to learn the chronic effects of marihuana inhalation.

Although the evidence linking marihuana with impaired liver function is questionable - in one human study the impairment seemed to be more closely related to previously denied alcohol use rather than marihuana - the effects of the drug on this vital organ are being studied. Since the liver plays an important role in metabolizing a number of drugs, the effects of cannabis on liver function may also significantly affect the action of these other drugs.

It is evident that many persons use not just marihuana but many other psychoactive drugs as well. Some of the reported toxic effects may well be the result of the interaction of cannabis with these other drugs. Almost certainly, as marihuana use spreads, it will be used concomitantly with still other drugs in addition to such common recreational drugs as alcohol and tobacco. Expanded efforts to examine some of these interactive effects are underway and more are planned.

To date the studies of chronic users have either been poorly controlled by modern scientific standards or limited to relatively small numbers of intensively studied users. The pilot efforts of the past year will be expanded and more extensive studies of larger populations of users are planned. Inherently, intensive studies of small samples have definite limitations. As studies of the effects of other drugs have clearly demonstrated, many serious effects can only be elucidated by the use of sizable samples. It is unlikely, for example, that the carcinogenic potential of cigarettes would have been demonstrated without the study of relatively large groups.

Although there have been many case reports of adverse effects, we are not certain just how common these are in user populations. Detailed epidemiological studies of the base rates of adverse physical and psychological reactions would be very valuable in gauging the health hazard posed by cannabis.

In the psychosocial realm a beginning has been made in improving our understanding of the drug user's career over time. Much expanded longitudinal studies would be very useful in helping us to better understand those aspects of development which effect patterns of marihuana consumption.

More needs to be learned about the social reinforcements of marihuana use including those factors influencing recruitment to drug use and those which encourage the individual to continue or to terminate such use. By better understanding some of these we may be able to be more effective in preventing use.

Little is presently known about the occupational and industrial implications of drug use including the use of cannabis. We do know that at least some cannabis users do so in the working situation. The effect of such use on industrial functioning including industrial safety badly needs to be examined.

A beginning has been made in determining some of the implications of marihuana use for driver performance. More needs to be learned in this vital area, and in particular the relationship between marihuana use and vehicular accidents should be explored. The development of a simple test for marihuana or its constituents in body fluids may prove to be an invaluable tool in evaluating its role in accidents.

Late in the past year a preliminary finding that marihuana may be implicated in brain atrophy was published. Although the study has many limitations and its authors caution against its overinterpretation, the seriousness of this finding obviously requires careful follow-up. Efforts are currently underway to study this possibility in primates and to encourage additional clinical work. As we become aware of other possible adverse implications of marihuana use through animal or human research, every effort is being expended to carefully study such findings under circumstances that will systematically examine their implications. In this respect animal and human research can effectively complement one another. The clinical observation can sometimes be more carefully studied in an animal model and the latter may provide useful clues to what might be systematically sought in clinical observation.

We have already commented on the fact that simple availability of marihuana may not be the most significant factor in its use and abuse. In the attempt to prevent abuse, social customs and controls, guided by informal knowledge, are far more potent than legal sanctions alone.

The barest of beginnings has been made in studying cross-cultural aspects of drug use. Although knowledge of those forces which affect drug use in other cultures may not be directly translatable into our own, it may provide some useful indicators of ways in which abuse can be controlled more effectively.

It is not as yet clear to what extent we have now or are likely to have a marihuana population of heavy users in need of or desirous of some form of treatment. As use further expands it is likely that such a population will, however, develop. Research is currently underway and more is planned to develop more effective behavior modification approaches to the "soft" drug user whether of marihuana or of multiple drugs.

Finally, our greatly increased understanding of the nature of cannabis and related synthetic materials has revived an interest in them as possible therapeutic agents. Such substances which may have rather low toxicity from a therapeutic standpoint should be further explored for their pharmaceutical value. One recently discovered possibility is that the effect of cannabis in reducing intraocular pressure may have significance in the treatment of glaucoma.

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